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## 3,5-DISUBSTITUTED 1H-PYRROLO[2,3-B]PYRIDINES AS JNK INHIBITORS

The present invention relates to novel compounds, their use in the inhibition of c-Jun N-terminal kinases, their use in medicine and particularly in the prevention and/or treatment of neurodegenerative disorders related to apoptosis and/or inflammation. The invention also provides processes for manufacture of said compounds, compositions containing them and processes for manufacturing such compositions.

10 c-Jun N-terminal kinases (hereinafter referred to as "JNKs") are members of the mitogen-activated protein kinase (MAPK) family. JNKs are involved in response to various stimuli, including proinflammatory cytokines and environmental stress. JNKs, and JNK3 in particular, play an important role during apoptotic death of cells and therefore have been implicated in various 15 disorders including stroke, traumatic brain injury and other neurodegenerative diseases such as Parkinson disease, Alzheimer disease and others. Since JNK activity is a physiological regulator of AP-1 transcriptional activity, JNK inhibitors are expected to reduce inflammatory response.

20 Apoptosis is a form of cell death in which the cell actively participates in its own destruction in a process involving a characteristic series of biochemical and morphological changes, which are regulated by specific cell death genes. The apoptotic cell death is a process that has been observed in the developing mammalian nervous system. In mice, the inactivation by homologous 25 recombination of genes that encode proteins that promote apoptosis, such as the caspase-3 or the Bax protein, prevents developmental neuronal cell death. The destruction of genes that encode cell death suppressors such as Bcl-x, leads to enhanced neuronal cell death. There is increasing evidence that apoptosis plays an important role in the pathology of acute and chronic neurodegenerative

diseases. For example, in transgenic mice overexpressing the anti-apoptotic Bcl-2 protein in the nervous system there is a decrease in infarct volume following cerebral ischemia. Similarly, injection of the caspase inhibitor BAP reduces neuronal cell death following hypoxia/ischaemia in neonatal rats.

5 Another example is spinal muscular atrophy (a motor neuron disease) where loss of function mutations in the SMN gene is associated with the disease. Recent data has shown that the wild type SMN protein binds to Bcl-2 and cooperates with it to inhibit apoptosis. These results suggest that inhibitors of neuronal apoptosis could be beneficial in the treatment of human

10 neurodegenerative diseases. There is increasing evidence that neuronal apoptosis is an important pathological feature of stroke, traumatic brain injury and other neurodegenerative diseases. Therefore, pharmacotherapy using inhibitors of neuronal apoptosis may provide a therapeutic benefit in neurodegenerative conditions.

15 A number of groups have studied the mechanisms of neuronal cell death using in vitro cell culture systems and the results suggest that in some systems the transcription factor c-Jun is activated by the removal of survival signals and promotes cell death.

20 Antibodies specific for c-Jun protected NGF-deprived rat sympathetic neurones from apoptosis. Analogous neuroprotection due to expression of a c-Jun dominant negative mutant has been demonstrated, whereas overexpression of wild type c-Jun protein was sufficient to induce apoptosis in the presence of

25 NGF. Estus and co-workers recently showed that an increase in c-Jun RNA levels occurs in cortical neurones undergoing apoptosis after treatment with  $\beta$ -amyloid peptide. It has also been shown that c-Jun is required for apoptosis in cerebellar granule neurones deprived of survival signals.

c-Jun is activated by JNKs, which phosphorylate its transcriptional activation domain. In humans there are three JNK genes: JNK1, JNK2 and JNK3. The RNAs encoding JNK1 and JNK2 are expressed in many tissues, including the brain, but JNK3 is restricted to the nervous system and to a smaller extent the 5 heart and testes.

JNKs are strongly activated in cellular responses to various stresses such as UV radiation, heat shock, osmotic shock, DNA-damaging agents, and proinflammatory cytokines such as TNF $\alpha$ , IL-1 $\beta$  and others. Upstream 10 regulators of the JNK pathway include kinases such as SEK1, MKK7 and MEKK1. There is evidence that Jun kinase activity is required for neuronal apoptosis in vitro. Overexpression of MEKK1 in sympathetic neurones increased c-Jun protein levels and phosphorylation and induced apoptosis in the presence of NGF indicating that activation of the Jun kinase pathway can 15 trigger neuronal cell death. The Jun kinase pathway has been shown to be necessary for the death of differentiated PC12 cells deprived of NGF. Furthermore, compound CEP-1347, which inhibits the c-Jun pathway (upstream of Jun kinase), protects motor neurones against cell death induced by survival factor withdrawal.

20 In JNK3 homozygous (-/-) knockout mice, epileptic seizures and death of hippocampal CA3 neurones induced by injection of kainic acid is blocked. This indicates that JNK3 is involved in certain forms of neuronal cell death in vivo. It is also a critical component of GluR6-mediated excitotoxicity. Furthermore, 25 JNK3 (-/-) mice appear to develop normally and are viable suggesting that JNK3 is not essential for development or viability.

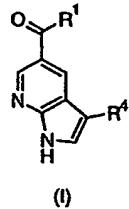
Strong nuclear JNK3 immunoreactivity in the brain CA1 neurones of patients with acute hypoxia suggests that JNK3 is involved in hypoxia-related

neurodegeneration. Transient hypoxia may also trigger apoptosis through JNK signaling pathway in developing brain neurones.

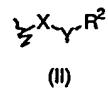
Furthermore, JNK3 immunoreactivity is colocalized with Alzheimer disease-  
5 affected neurones. Moreover JNK3 is related to neurofibrillary pathology of Alzheimer disease. In particular, JNK3 induces robust phosphorylation of amyloid precursor protein (APP) thus affecting its metabolism in disease state.

The present inventors have provided compounds, which are inhibitors of c-Jun  
10 N-terminal kinases.

The first aspect of the invention therefore relates to a compound of formula (I)  
as illustrated below:



15 wherein R<sup>1</sup> is an optionally substituted C<sub>3-12</sub> carbocyclyl or C<sub>3-12</sub> heterocyclyl group or a group of formula (II)



wherein X is NR<sup>3</sup>, O, S or (CR<sup>22</sup>R<sup>22</sup>)<sub>n</sub>, Y is absent or is NR<sup>23</sup>, O, or (CR<sup>23</sup>R<sup>23</sup>)<sub>n</sub>,  
20 R<sup>2</sup> is optionally substituted C<sub>1-12</sub> alkyl, C<sub>2-12</sub> alkenyl, C<sub>2-12</sub> alkynyl, C<sub>3-12</sub> carbocyclyl or C<sub>3-12</sub> heterocyclyl, and R<sup>4</sup> is an optionally substituted five or six membered heterocyclyl group or an optionally substituted six membered carbocyclyl group;

wherein the optionally substituted carbocyclyl or heterocyclyl group of  $R^1$  is optionally fused to a partially saturated, unsaturated or fully saturated five to seven membered ring containing zero to three heteroatoms, and each substitutable carbon atom in  $R^1$ , including the optional fused ring, is optionally 5 and independently substituted by one or more of halogen,  $C_{1-12}$  alkyl,  $C_{2-12}$  alkenyl,  $C_{2-12}$  alkynyl, halo $C_{1-12}$ alkyl,  $C_{3-12}$  carbocyclyl,  $C_{3-12}$  heterocyclyl,  $(CH_2)_nOR^5$ ,  $(CH_2)_nNR^5_2(CH_2)_nSR^5$ ,  $OR^5$ ,  $SR^5$ ,  $NO_2$ ,  $CN$ ,  $NR^5_2$ ,  $NR^5COR^5$ ,  $NR^5CONR^5_2$ ,  $NR^5COR^5$ ,  $NR^5CO_2R^5$ ,  $CO_2R^5$ ,  $COR^5$ ,  $CONR^5_2$ ,  $S(O)_2R^5$ ,  $SONR^5_2$ ,  $S(O)R^5$ ,  $SO_2NR^5_2$ , or  $NR^5S(O)_2R^5$  wherein the  $C_{1-12}$  alkyl group 10 optionally contains one or more insertions selected from  $-O-$ ,  $-N(R^5)-$ ,  $-S-$ ,  $-S(O)-$  and  $-S(O_2)-$ ; and each saturated carbon in the optional fused ring is further optionally and independently substituted by  $=O$ ,  $=S$ ,  $NNR^6_2$ ,  $=N-OR^6$ ,  $=NNR^6COR^6$ ,  $=NNR^6CO_2R^6$ ,  $=NNSO_2R^6$ , or  $=NR^6$ ; and each substitutable nitrogen atom in  $R^1$  is optionally substituted by  $R^7$ ,  $COR^7$ ,  $SO_2R^7$  or  $CO_2R^7$ ;

15 wherein  $n$  is 1 to 6, preferably  $n$  is 1, 2 or 3;

wherein  $R^5$  is hydrogen,  $C_{1-12}$  alkyl,  $C_{3-12}$  carbocyclyl or  $C_{3-12}$  heterocyclyl, optionally substituted by one or more of  $C_{1-6}$  alkyl,  $C_{3-12}$  carbocyclyl,  $C_{3-12}$  heterocyclyl, halogen,  $C_{1-6}$  haloalkyl,  $OR^8$ ,  $SR^8$ ,  $NO_2$ ,  $CN$ ,  $NR^8R^8$ ,  $NR^8COR^8$ , 20  $NR^8CONR^8R^8$ ,  $NR^8COR^8$ ,  $NR^8CO_2R^8$ ,  $CO_2R^8$ ,  $COR^8$ ,  $CONR^8_2$ ,  $S(O)_2R^8$ ,  $SONR^8_2$ ,  $S(O)R^8$ ,  $SO_2NR^8R^8$ ,  $NR^8S(O)_2R^8$ , wherein the  $C_{1-12}$  alkyl group optionally incorporates one or two insertions selected from the group consisting of  $-O-$ ,  $-N(R^8)-$ ,  $-S(O)-$  and  $-S(O_2)-$ , wherein each  $R^8$  may be the same or different and is as defined below;

25 wherein two  $R^5$  in  $NR^5_2$  may optionally form a partially saturated, unsaturated or fully saturated three to seven membered ring containing one to three heteroatoms, optionally and independently substituted by one or more of  $C_{1-6}$  alkyl, halogen,  $C_{1-6}$  haloalkyl,  $OR^8$ ,  $SR^8$ ,  $NO_2$ ,  $CN$ ,  $NR^8R^8$ ,  $NR^8COR^8$ ,

NR<sup>8</sup>CONR<sup>8</sup>R<sup>8</sup>, NR<sup>8</sup>COR<sup>8</sup>, NR<sup>8</sup>CO<sub>2</sub>R<sup>8</sup>, CO<sub>2</sub>R<sup>8</sup>, COR<sup>8</sup>, CONR<sup>8</sup><sub>2</sub>, S(O)<sub>2</sub>R<sup>8</sup>, SONR<sup>8</sup><sub>2</sub>, S(O)R<sup>8</sup>, SO<sub>2</sub>NR<sup>8</sup>R<sup>8</sup>, NR<sup>8</sup>S(O)<sub>2</sub>R<sup>8</sup>,

wherein the C<sub>1-6</sub> alkyl group optionally incorporates one or two insertions selected from the group consisting of -O-, -N(R<sup>8</sup>)-, -S(O)- and -S(O<sub>2</sub>)-, wherein

5 each R<sup>8</sup> may be the same or different and is as defined below;

wherein R<sup>6</sup> is hydrogen, C<sub>1-12</sub> alkyl, C<sub>3-12</sub> carbocyclyl or C<sub>3-12</sub> heterocyclyl, optionally substituted by one or more of C<sub>1-6</sub> alkyl, halogen, C<sub>1-6</sub> haloalkyl, OR<sup>8</sup>, SR<sup>8</sup>, NO<sub>2</sub>, CN, NR<sup>8</sup>R<sup>8</sup>, NR<sup>8</sup>COR<sup>8</sup>, NR<sup>8</sup>CONR<sup>8</sup>R<sup>8</sup>, NR<sup>8</sup>COR<sup>8</sup>, NR<sup>8</sup>CO<sub>2</sub>R<sup>8</sup>,

10 CO<sub>2</sub>R<sup>8</sup>, COR<sup>8</sup>, CONR<sup>8</sup><sub>2</sub>, S(O)<sub>2</sub>R<sup>8</sup>, S(O)R<sup>8</sup>, SO<sub>2</sub>NR<sup>8</sup>R<sup>8</sup>, NR<sup>8</sup>S(O)<sub>2</sub>R<sup>8</sup>, wherein the C<sub>1-12</sub> alkyl group optionally incorporates one or two insertions selected from the group consisting of -O-, -N(R<sup>8</sup>)-, -S(O)- and -S(O<sub>2</sub>)-, wherein each R<sup>8</sup> may be the same or different and is as defined below;

15 wherein R<sup>7</sup> is hydrogen, C<sub>6-12</sub> aryl, C<sub>1-6</sub> alkyl or C<sub>1-6</sub> haloalkyl;

wherein R<sup>8</sup> is hydrogen, C<sub>1-6</sub> alkyl, or C<sub>1-6</sub> haloalkyl;

Y is absent or is NR<sup>23</sup>, O, or (CR<sup>23</sup>R<sup>23</sup>)<sub>n</sub>, wherein each R<sup>23</sup> may be the same or

20 different and is H, C<sub>1-4</sub> alkyl, C<sub>1-4</sub> alkoxy or C<sub>1-4</sub> haloalkyl;

and n is 1 to 6, preferably n is 1, 2, 3 or 4.

R<sup>2</sup> is C<sub>1-12</sub> alkyl, C<sub>2-12</sub> alkenyl, C<sub>2-12</sub> alkynyl, C<sub>3-12</sub> carbocyclyl or C<sub>3-12</sub> heterocyclyl, each of which is optionally substituted, wherein:

25 the optionally substituted carbocyclyl or heterocyclyl group is optionally fused to one to three unsaturated, partially unsaturated or fully saturated five to seven membered rings containing zero to three heteroatoms;

each substitutable carbon atom in R<sup>2</sup>, including the optional fused ring, is optionally and independently substituted by one or more of C<sub>1-12</sub> alkyl, C<sub>3-12</sub>

cycloalkyl, C<sub>3-12</sub> heterocycloalkyl, C<sub>3-12</sub> aryl, C<sub>3-12</sub> heteroaryl halogen, C<sub>1-12</sub> haloalkyl, OR<sup>9</sup>, SR<sup>9</sup>, NO<sub>2</sub>, CN, NR<sup>9</sup>R<sup>9</sup>, NR<sup>9</sup>COR<sup>9</sup>, NR<sup>9</sup>CONR<sup>9</sup>R<sup>9</sup>, NR<sup>9</sup>COR<sup>9</sup>, NR<sup>9</sup>CO<sub>2</sub>R<sup>9</sup>, CO<sub>2</sub>R<sup>9</sup>, COR<sup>9</sup>, CONR<sup>9</sup>R<sup>9</sup>, S(O)<sub>2</sub>R<sup>9</sup>, SONH<sub>2</sub>, S(O)R<sup>9</sup>, SO<sub>2</sub>NR<sup>9</sup>R<sup>9</sup>, NR<sup>9</sup>S(O)<sub>2</sub>R<sup>9</sup>, wherein each R<sup>9</sup> may be the same or different and is as defined

5 below and wherein:

the C<sub>1-12</sub> alkyl group optionally incorporates one or two insertions selected from the group consisting of -O-, -C(O)-, -N(R<sup>9</sup>)-, -S(O)- and -S(O<sub>2</sub>)-, wherein each R<sup>9</sup> may be the same or different and is as defined above;

the C<sub>1-12</sub> alkyl, C<sub>3-12</sub> cycloalkyl, C<sub>3-12</sub> heterocycloalkyl, C<sub>3-12</sub> aryl, or C<sub>3-12</sub> heteroaryl groups are optionally substituted by one or more of halogen, C<sub>1-12</sub> haloalkyl, OR<sup>9</sup>, SR<sup>9</sup>, NO<sub>2</sub>, CN, NR<sup>9</sup>R<sup>9</sup>, NR<sup>9</sup>COR<sup>9</sup>, NR<sup>9</sup>CONR<sup>9</sup>R<sup>9</sup>, NR<sup>9</sup>COR<sup>9</sup>, NR<sup>9</sup>CO<sub>2</sub>R<sup>9</sup>, CO<sub>2</sub>R<sup>9</sup>, COR<sup>9</sup>, CONR<sup>9</sup>R<sup>9</sup>, S(O)<sub>2</sub>R<sup>9</sup>, SONH<sub>2</sub>, S(O)R<sup>9</sup>, SO<sub>2</sub>NR<sup>9</sup>R<sup>9</sup>, NR<sup>9</sup>S(O)<sub>2</sub>R<sup>9</sup>, wherein each R<sup>9</sup> may be the same or different and is as defined below; and

15 the C<sub>3-12</sub> cycloalkyl, C<sub>3-12</sub> heterocycloalkyl, C<sub>3-12</sub> aryl, or C<sub>3-12</sub> heteroaryl groups are optionally substituted by one or more C<sub>1-12</sub> alkyl groups;

each saturated carbon in R<sup>2</sup>, including the optional fused ring, is further optionally and independently substituted by =O, =S, NNR<sup>9</sup>R<sup>9</sup>, =N-OR<sup>9</sup>, =NNHCOR<sup>9</sup>, =NNHCO<sub>2</sub>R<sup>9</sup>, =NNSO<sub>2</sub>R<sup>9</sup>, or =NR<sup>9</sup>, wherein each R<sup>9</sup> may be the

20 same or different and is as defined below; and

each substitutable nitrogen atom in R<sup>2</sup> is optionally substituted by R<sup>10</sup>, COR<sup>9</sup>, SO<sub>2</sub>R<sup>9</sup> or CO<sub>2</sub>R<sup>9</sup> wherein each R<sup>9</sup> and R<sup>10</sup> may be the same or different and is as defined below;

25 wherein two R<sup>9</sup> in NR<sup>9</sup><sub>2</sub> may optionally form a partially saturated, unsaturated or fully saturated three to seven membered ring containing one to three

heteroatoms, optionally and independently substituted by one or more of C<sub>1-6</sub> alkyl, halogen, C<sub>1-6</sub> haloalkyl, OR<sup>11</sup>, SR<sup>11</sup>, NO<sub>2</sub>, CN, NR<sup>11</sup>R<sup>11</sup>, NR<sup>11</sup>COR<sup>11</sup>, NR<sup>11</sup>CONR<sup>11</sup>R<sup>11</sup>, NR<sup>11</sup>COR<sup>11</sup>, NR<sup>11</sup>CO<sub>2</sub>R<sup>11</sup>, CO<sub>2</sub>R<sup>11</sup>, COR<sup>11</sup>, CONR<sup>11</sup><sub>2</sub>, S(O)<sub>2</sub>R<sup>11</sup>, SONR<sup>11</sup><sub>2</sub>, S(O)R<sup>11</sup>, SO<sub>2</sub>NR<sup>11</sup>R<sup>11</sup>, NR<sup>11</sup>S(O)<sub>2</sub>R<sup>11</sup>,

wherein the C<sub>1-6</sub> alkyl group optionally incorporates one or two insertions selected from the group consisting of -O-, -N(R<sup>11</sup>)-, -S(O)- and -S(O<sub>2</sub>)-, wherein each R<sup>11</sup> may be the same or different and is as defined below; wherein R<sup>11</sup> is hydrogen, C<sub>1-6</sub> alkyl, or C<sub>1-6</sub> haloalkyl;

5

wherein R<sup>9</sup> is hydrogen, C<sub>1-12</sub> alkyl or C<sub>3-12</sub> aryl, optionally substituted by one or more of C<sub>1-4</sub> alkyl, halogen, C<sub>1-4</sub> haloalkyl, OR<sup>12</sup>, SR<sup>12</sup>, NO<sub>2</sub>, CN, NR<sup>12</sup>R<sup>12</sup>, NR<sup>12</sup>COR<sup>12</sup>, NR<sup>12</sup>CONR<sup>12</sup>R<sup>12</sup>, NR<sup>12</sup>COR<sup>12</sup>, NR<sup>12</sup>CO<sub>2</sub>R<sup>12</sup>, CO<sub>2</sub>R<sup>12</sup>, COR<sup>12</sup>, CONR<sup>12</sup><sub>2</sub>, S(O)<sub>2</sub>R<sup>12</sup>, SONH<sub>2</sub>, S(O)R<sup>12</sup>, SO<sub>2</sub> NR<sup>12</sup>R<sup>12</sup>, NR<sup>12</sup>S(O)<sub>2</sub>R<sup>12</sup>, wherein

10 the C<sub>1-12</sub> alkyl group optionally incorporates one or two insertions selected from the group consisting of -O-, -N(R<sup>12</sup>)-, -S(O)- and -S(O<sub>2</sub>)-, wherein each R<sup>12</sup> may be the same or different and is as defined below;

wherein R<sup>10</sup> is C<sub>1-12</sub> alkyl or C<sub>3-12</sub> aryl, optionally substituted by one or more of  
 15 C<sub>1-4</sub> alkyl, halogen, C<sub>1-4</sub> haloalkyl, OR<sup>12</sup>, SR<sup>12</sup>, NO<sub>2</sub>, CN, NR<sup>12</sup>R<sup>12</sup>, NR<sup>12</sup>COR<sup>12</sup>, NR<sup>12</sup>CONR<sup>12</sup>R<sup>12</sup>, NR<sup>12</sup>COR<sup>12</sup>, NR<sup>12</sup>CO<sub>2</sub>R<sup>12</sup>, CO<sub>2</sub>R<sup>12</sup>, COR<sup>12</sup>, CONR<sup>12</sup><sub>2</sub>, S(O)<sub>2</sub>R<sup>12</sup>, SONH<sub>2</sub>, S(O)R<sup>12</sup>, SO<sub>2</sub>NR<sup>12</sup>R<sup>12</sup>, NR<sup>12</sup>S(O)<sub>2</sub>R<sup>12</sup>, wherein the C<sub>1-12</sub> alkyl group optionally incorporates one or two insertions selected from the group consisting of -O-, -N(R<sup>12</sup>)-, -S(O)- and -S(O<sub>2</sub>)-, wherein each R<sup>12</sup> may be the  
 20 same or different and is as defined below;

wherein R<sup>12</sup> is hydrogen, C<sub>1-4</sub> alkyl, or C<sub>1-4</sub> haloalkyl;

X is NR<sup>3</sup>; O, S or (CR<sup>22</sup>R<sup>22</sup>)<sub>n</sub> wherein R<sup>22</sup> is independently one or more of  
 25 halogen, C<sub>1-12</sub> alkyl, C<sub>2-12</sub> alkenyl, C<sub>2-12</sub> alkynyl, C<sub>1-12</sub> haloalkyl, C<sub>6-12</sub> carbocyclyl, C<sub>5-12</sub> heterocyclyl, (CH<sub>2</sub>)<sub>n</sub>OR<sup>5</sup>, (CH<sub>2</sub>)<sub>n</sub>NR<sup>5</sup><sub>2</sub>, OR<sup>5</sup>, SR<sup>5</sup>, NO<sub>2</sub>, CN, NR<sup>5</sup><sub>2</sub>, NR<sup>5</sup>COR<sup>5</sup>, NR<sup>5</sup>CONR<sup>5</sup><sub>2</sub>, NR<sup>5</sup>COR<sup>5</sup>, NR<sup>5</sup>CO<sub>2</sub>R<sup>5</sup>, CO<sub>2</sub>R<sup>5</sup>, COR<sup>5</sup>, CONR<sup>5</sup><sub>2</sub>, S(O)<sub>2</sub>R<sup>5</sup>, SONR<sup>5</sup><sub>2</sub>, S(O)R<sup>5</sup>, SO<sub>2</sub>NR<sup>5</sup><sub>2</sub>, or NR<sup>5</sup>S(O)<sub>2</sub>R<sup>5</sup> wherein each R<sup>5</sup> may be the same or different and is as defined above; and

wherein n is 1 to 6, preferably n is 1, 2, 3 or 4;

wherein  $R^3$  is a lone electron pair, hydrogen,  $C_{1-12}$  alkyl,  $C_{2-12}$  alkenyl,  $C_{2-12}$

alkynyl,  $C_{3-12}$  carbocyclyl or  $C_{3-12}$  heterocyclyl, each of which is optionally

5 substituted, wherein:

the optionally substituted carbocyclyl or heterocyclyl group is optionally fused to one to three unsaturated, partially unsaturated or fully saturated five to seven membered rings containing zero to three heteroatoms,

each substitutable carbon atom in  $R^3$ , including the optional fused ring, is

10 optionally and independently substituted by one or more of  $C_{1-12}$  alkyl,  $C_{3-12}$  cycloalkyl,  $C_{3-12}$  heterocycloalkyl,  $C_{3-12}$  aryl,  $C_{3-12}$  heteroaryl halogen,  $C_{1-12}$  haloalkyl,  $OR^{13}$ ,  $SR^{13}$ ,  $NO_2$ ,  $CN$ ,  $NR^{13}R^{13}$ ,  $NR^{13}COR^{13}$ ,  $NR^{13}CONR^{13}R^{13}$ ,  $NR^{13}COR^{13}$ ,  $NR^{13}CO_2R^{13}$ ,  $CO_2R^{13}$ ,  $COR^{13}$ ,  $CONR^{13}R^{13}$ ,  $S(O)_2R^{13}$ ,  $SONH_2$ ,  $S(O)R^{13}$ ,  $SO_2NR^{13}R^{13}$ ,  $NR^{13}S(O)_2R^{13}$ , wherein each  $R^{13}$  may be the same or

15 different and is as defined above and wherein:

the  $C_{1-12}$  alkyl group optionally incorporates one or two insertions selected from the group consisting of -O-, -C(O)-, -N( $R^{13}$ )-, -S(O)- and -S( $O_2$ )-, wherein each  $R^{13}$  may be the same or different and is as defined above;

the  $C_{1-12}$  alkyl,  $C_{3-12}$  cycloalkyl,  $C_{3-12}$  heterocycloalkyl,  $C_{3-12}$  aryl, or  $C_{3-12}$

20 heteroaryl groups are optionally substituted by one or more of halogen,  $C_{1-12}$  haloalkyl,  $OR^{13}$ ,  $SR^{13}$ ,  $NO_2$ ,  $CN$ ,  $NR^{13}R^{13}$ ,  $NR^{13}COR^{13}$ ,  $NR^{13}CONR^{13}R^{13}$ ,  $NR^{13}COR^{13}$ ,  $NR^{13}CO_2R^{13}$ ,  $CO_2R^{13}$ ,  $COR^{13}$ ,  $CONR^{13}R^{13}$ ,  $S(O)_2R^{13}$ ,  $SONH_2$ ,  $S(O)R^{13}$ ,  $SO_2NR^{13}R^{13}$ ,  $NR^{13}S(O)_2R^{13}$ , wherein each  $R^{13}$  may be the same or different and is as defined below; and

25 the  $C_{3-12}$  cycloalkyl,  $C_{3-12}$  heterocycloalkyl,  $C_{3-12}$  aryl, or  $C_{3-12}$  heteroaryl groups are optionally substituted by one or more  $C_{1-12}$  alkyl groups; each saturated carbon in  $R^2$ , including the optional fused ring, is further optionally and independently substituted by =O, =S,  $NNR^{13}R^{13}$ , =N-OR<sup>13</sup>,

=NNHCOR<sup>13</sup>, =NNHCO<sub>2</sub>R<sup>13</sup>, =NNSO<sub>2</sub>R<sup>13</sup>, or =NR<sup>13</sup>, wherein each R<sup>13</sup> may be the same or different and is as defined below; and each substitutable nitrogen atom in R<sup>3</sup> is optionally substituted by R<sup>14</sup>, COR<sup>13</sup>, SO<sub>2</sub>R<sup>13</sup> or CO<sub>2</sub>R<sup>13</sup> wherein each R<sup>13</sup> and R<sup>14</sup> may be the same or different and is

5 as defined below;

wherein two R<sup>13</sup> in NR<sup>13</sup><sub>2</sub> may optionally form a partially saturated, unsaturated or fully saturated three to seven membered ring containing one to three heteroatoms, optionally and independently substituted by one or more of C<sub>1-6</sub> alkyl, halogen, C<sub>1-6</sub> haloalkyl, OR<sup>15</sup>, SR<sup>15</sup>, NO<sub>2</sub>, CN, NR<sup>15</sup>R<sup>15</sup>, NR<sup>15</sup>COR<sup>15</sup>,

10 NR<sup>15</sup>CONR<sup>15</sup>R<sup>15</sup>, NR<sup>15</sup>COR<sup>15</sup>, NR<sup>15</sup>CO<sub>2</sub>R<sup>15</sup>, CO<sub>2</sub>R<sup>15</sup>, COR<sup>15</sup>, CONR<sup>15</sup><sub>2</sub>, S(O)<sub>2</sub>R<sup>15</sup>, SONR<sup>15</sup><sub>2</sub>, S(O)R<sup>15</sup>, SO<sub>2</sub>NR<sup>15</sup>R<sup>15</sup>, NR<sup>15</sup>S(O)<sub>2</sub>R<sup>15</sup>, wherein the C<sub>1-6</sub> alkyl group optionally incorporates one or two insertions selected from the group consisting of -O-, -N(R<sup>15</sup>)-, -S(O)- and -S(O<sub>2</sub>)-, wherein each R<sup>15</sup> may be the same or different and is as defined below;

15 wherein R<sup>15</sup> is hydrogen, C<sub>1-6</sub> alkyl, or C<sub>1-6</sub> haloalkyl;

wherein R<sup>13</sup> is hydrogen, C<sub>1-12</sub> alkyl or C<sub>3-12</sub> aryl, optionally substituted by one or more of C<sub>1-4</sub> alkyl, halogen, C<sub>1-4</sub> haloalkyl, OR<sup>16</sup>, SR<sup>16</sup>, NO<sub>2</sub>, CN, NR<sup>16</sup>R<sup>16</sup>, NR<sup>16</sup>COR<sup>16</sup>, NR<sup>16</sup>CONR<sup>16</sup>R<sup>16</sup>, NR<sup>16</sup>COR<sup>16</sup>, NR<sup>16</sup>CO<sub>2</sub>R<sup>16</sup>, CO<sub>2</sub>R<sup>16</sup>, COR<sup>16</sup>,

20 CONR<sup>16</sup><sub>2</sub>, S(O)<sub>2</sub>R<sup>16</sup>, SONH<sub>2</sub>, S(O)R<sup>16</sup>, SO<sub>2</sub>NR<sup>16</sup>R<sup>16</sup>, NR<sup>16</sup>S(O)<sub>2</sub>R<sup>16</sup>, wherein the C<sub>1-12</sub> alkyl group optionally incorporates one or two insertions selected from the group consisting of -O-, -N(R<sup>16</sup>)-, -S(O)- and -S(O<sub>2</sub>)-, wherein each R<sup>16</sup> may be the same or different and is as defined below;

25 wherein R<sup>14</sup> is C<sub>1-12</sub> alkyl or C<sub>3-12</sub> aryl, optionally substituted by one or more of C<sub>1-4</sub> alkyl, halogen, C<sub>1-4</sub> haloalkyl, OR<sup>16</sup>, SR<sup>16</sup>, NO<sub>2</sub>, CN, NR<sup>16</sup>R<sup>16</sup>, NR<sup>16</sup>COR<sup>16</sup>, NR<sup>16</sup>CONR<sup>16</sup>R<sup>16</sup>, NR<sup>16</sup>COR<sup>16</sup>, NR<sup>16</sup>CO<sub>2</sub>R<sup>16</sup>, CO<sub>2</sub>R<sup>16</sup>, COR<sup>16</sup>, CONR<sup>16</sup><sub>2</sub>, S(O)<sub>2</sub>R<sup>16</sup>, SONH<sub>2</sub>, S(O)R<sup>16</sup>, SO<sub>2</sub>NR<sup>16</sup>R<sup>16</sup>, NR<sup>16</sup>S(O)<sub>2</sub>R<sup>16</sup>, wherein the C<sub>1-12</sub> alkyl group optionally incorporates one or two insertions selected from the group

consisting of -O-, -N(R<sup>16</sup>)-, -S(O)- and -S(O<sub>2</sub>)-, wherein each R<sup>16</sup> may be the same or different and is as defined below;

wherein R<sup>16</sup> is hydrogen, C<sub>1-4</sub> alkyl, or C<sub>1-4</sub> haloalkyl;

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wherein when X is NR<sup>2</sup>, R<sup>2</sup> and R<sup>3</sup> can form a 3 to 12 membered heterocyclyl ring, more preferably a 5, 6, 7, 8, 9, 10, 11 or 12 membered ring, wherein said ring can be partially saturated, unsaturated or fully saturated containing one to three heteroatoms; wherein the heterocyclic group formed by R<sup>2</sup> and R<sup>3</sup> can 10 be optionally fused to one to three unsaturated, partially saturated or fully saturated 5 to 7 membered rings and contains from zero to three heteroatoms, any of said rings being optionally and independently substituted with one or more of C<sub>1-6</sub> alkyl, halogen, C<sub>1-6</sub> haloalkyl, OR<sup>22</sup>, SR<sup>22</sup>, NO<sub>2</sub>, CN, NR<sup>22</sup>R<sup>22</sup>, NR<sup>22</sup>COR<sup>22</sup>, NR<sup>22</sup>CONR<sup>22</sup>R<sup>22</sup>, NR<sup>22</sup>COR<sup>22</sup>, NR<sup>22</sup>CO<sub>2</sub>R<sup>22</sup>, CO<sub>2</sub>R<sup>22</sup>, COR<sup>22</sup>, 15 CONR<sup>22</sup><sub>2</sub>, S(O)R<sup>22</sup>, SONR<sup>22</sup><sub>2</sub>, S(O)R<sup>22</sup>, SO<sub>2</sub>NR<sup>22</sup>R<sup>22</sup>, NR<sup>22</sup>S(O)R<sup>22</sup>, wherein the C<sub>1-6</sub> alkyl group optionally incorporates one or two insertions from -O-, -N(R<sup>22</sup>)-, -S(O)- and -S(O<sub>2</sub>)- and wherein each R<sup>22</sup> may be the same or different;

and wherein R<sup>4</sup> is a six-membered carbocyclyl group or a five or six-membered 20 heterocyclyl group containing from 1 to 4 heteroatoms independently selected from N, S or O, wherein the optionally substituted six-membered carbocyclyl or five or six-membered heterocyclyl group is optionally fused to a partially saturated, unsaturated or fully saturated five to seven membered ring containing zero to three heteroatoms, and each substitutable carbon or hetero-atom in R<sup>4</sup> 25 including the optional fused ring, is optionally and independently substituted by one or more of halogen, C<sub>1-12</sub> alkyl, C<sub>2-12</sub> alkenyl, C<sub>2-12</sub> alkynyl, C<sub>1-12</sub> haloalkyl, C<sub>3-12</sub> carbocyclyl, C<sub>3-12</sub> heterocyclyl, (CH<sub>2</sub>)<sub>n</sub>OR<sup>17</sup>, (CH<sub>2</sub>)<sub>n</sub>NR<sup>17</sup><sub>2</sub>, OR<sup>17</sup>, SR<sup>17</sup>, NO<sub>2</sub>, CN, NR<sup>17</sup><sub>2</sub>, NR<sup>17</sup>COR<sup>17</sup>, NR<sup>17</sup>CONR<sup>17</sup><sub>2</sub>, NR<sup>17</sup>COR<sup>17</sup>, NR<sup>17</sup>CO<sub>2</sub>R<sup>17</sup>, CO<sub>2</sub>R<sup>17</sup>, COR<sup>17</sup>, CONR<sup>17</sup><sub>2</sub>, S(O)R<sup>17</sup>, SONR<sup>17</sup><sub>2</sub>, S(O)R<sup>17</sup>, SO<sub>2</sub>NR<sup>17</sup><sub>2</sub>, or

NR<sup>17</sup>S(O)<sub>2</sub>R<sup>17</sup>, wherein the C<sub>1-12</sub> alkyl group optionally contains one or more insertions selected from -O-, -N(R<sup>12</sup>)-, -S-, -S(O)- and -S(O<sub>2</sub>)-; and each saturated carbon in the optional fused ring is further optionally and independently substituted by =O, =S, NNR<sup>18</sup><sub>2</sub>, =N-OR<sup>18</sup>, =NNR<sup>18</sup>COR<sup>18</sup>, =NNR<sup>18</sup>CO<sub>2</sub>R<sup>18</sup>, =NNSO<sub>2</sub>R<sup>18</sup>, or =NR<sup>18</sup>; and each substitutable nitrogen atom in R<sup>4</sup> is optionally substituted by R<sup>19</sup>, COR<sup>19</sup>, SO<sub>2</sub>R<sup>19</sup> or CO<sub>2</sub>R<sup>19</sup>; wherein n is 1 to 6, preferably n is 1, 2 or 3; preferably, wherein each substitutable carbon or hetero-atom in R<sup>4</sup> is optionally and independently substituted by one or more of C<sub>1-6</sub> alkyl, OR<sup>20</sup>, SR<sup>20</sup>, NO<sub>2</sub>, CN, NR<sup>20</sup><sub>2</sub>, NR<sup>20</sup>COR<sup>20</sup>, NR<sup>20</sup>CONR<sup>20</sup><sub>2</sub>, NR<sup>20</sup>COR<sup>20</sup>, NHCO<sub>2</sub>R<sup>20</sup>, CO<sub>2</sub>R<sup>20</sup>, COR<sup>20</sup>, CONR<sup>20</sup><sub>2</sub>, S(O)<sub>2</sub>R<sup>20</sup>, SONR<sup>20</sup><sub>2</sub>, S(O)R<sup>20</sup>, SO<sub>2</sub>NR<sup>20</sup><sub>2</sub>, or NR<sup>20</sup>S(O)<sub>2</sub>R<sup>20</sup>;

wherein R<sup>20</sup> is hydrogen, C<sub>1-6</sub> alkyl, or C<sub>1-6</sub> haloalkyl;

15 wherein R<sup>17</sup> is hydrogen, C<sub>1-12</sub> alkyl, C<sub>3-12</sub> carbocyclyl or C<sub>3-12</sub> heterocyclyl, optionally substituted by one or more of C<sub>1-6</sub> alkyl, C<sub>3-12</sub> carbocyclyl, C<sub>3-12</sub> heterocyclyl, halogen, C<sub>1-6</sub> haloalkyl, OR<sup>21</sup>, SR<sup>21</sup>, NO<sub>2</sub>, CN, NR<sup>21</sup>R<sup>21</sup>, NR<sup>21</sup>COR<sup>21</sup>, NR<sup>21</sup>CONR<sup>21</sup>R<sup>21</sup>, NR<sup>21</sup>COR<sup>21</sup>, NR<sup>21</sup>CO<sub>2</sub>R<sup>21</sup>, CO<sub>2</sub>R<sup>21</sup>, COR<sup>21</sup>, CONR<sup>21</sup><sub>2</sub>, S(O)<sub>2</sub>R<sup>21</sup>, SONR<sup>21</sup><sub>2</sub>, S(O)R<sup>21</sup>, SO<sub>2</sub>NR<sup>21</sup>R<sup>21</sup>, NR<sup>21</sup>S(O)<sub>2</sub>R<sup>21</sup>, wherein 20 the C<sub>1-12</sub> alkyl group optionally incorporates one or two insertions selected from the group consisting of -O-, -N(R<sup>21</sup>)-, -S(O)- and -S(O<sub>2</sub>)-, wherein each R<sup>21</sup> may be the same or different and is as defined below;

wherein two R<sup>17</sup> in NR<sup>17</sup><sub>2</sub> may optionally form a partially saturated, unsaturated 25 or fully saturated three to seven membered ring containing one to three heteroatoms, optionally and independently substituted by one or more of C<sub>1-6</sub> alkyl, halogen, C<sub>1-6</sub> haloalkyl, OR<sup>21</sup>, SR<sup>21</sup>, NO<sub>2</sub>, CN, NR<sup>21</sup>R<sup>21</sup>, NR<sup>21</sup>COR<sup>21</sup>, NR<sup>21</sup>CONR<sup>21</sup>R<sup>21</sup>, NR<sup>21</sup>COR<sup>21</sup>, NR<sup>21</sup>CO<sub>2</sub>R<sup>21</sup>, CO<sub>2</sub>R<sup>21</sup>, COR<sup>21</sup>, CONR<sup>21</sup><sub>2</sub>, S(O)<sub>2</sub>R<sup>21</sup>, SONR<sup>21</sup><sub>2</sub>, S(O)R<sup>21</sup>, SO<sub>2</sub>NR<sup>21</sup>R<sup>21</sup>, NR<sup>21</sup>S(O)<sub>2</sub>R<sup>21</sup>, wherein the C<sub>1-6</sub>

alkyl group optionally incorporates one or two insertions selected from the group consisting of -O-, -N(R<sup>21</sup>)-, -S(O)- and -S(O<sub>2</sub>)-, wherein each R<sup>21</sup> may be the same or different and is as defined below;

5 wherein R<sup>18</sup> is hydrogen, C<sub>1-12</sub> alkyl, C<sub>3-12</sub> carbocyclyl or C<sub>3-12</sub> heterocyclyl, optionally substituted by one or more of C<sub>1-6</sub> alkyl, halogen, C<sub>1-6</sub> haloalkyl, OR<sup>21</sup>, SR<sup>21</sup>, NO<sub>2</sub>, CN, NR<sup>21</sup>R<sup>21</sup>, NR<sup>21</sup>COR<sup>21</sup>, NR<sup>21</sup>CONR<sup>21</sup>R<sup>21</sup>, NR<sup>21</sup>COR<sup>21</sup>, NR<sup>21</sup>CO<sub>2</sub>R<sup>21</sup>, CO<sub>2</sub>R<sup>21</sup>, COR<sup>21</sup>, CONR<sup>21</sup><sub>2</sub>, S(O)<sub>2</sub>R<sup>21</sup>, S(O)R<sup>21</sup>, SO<sub>2</sub>NR<sup>21</sup>R<sup>21</sup>, NR<sup>21</sup>S(O)<sub>2</sub>R<sup>21</sup>, wherein the C<sub>1-12</sub> alkyl group optionally incorporates one or two  
10 insertions selected from the group consisting of -O-, -N(R<sup>21</sup>)-, -S(O)- and -S(O<sub>2</sub>)-, wherein each R<sup>21</sup> may be the same or different and is as defined below;

wherein R<sup>19</sup> is hydrogen, C<sub>6-12</sub> aryl, C<sub>1-6</sub> alkyl or C<sub>1-6</sub> haloalkyl;

wherein R<sup>21</sup> is hydrogen, C<sub>1-6</sub> alkyl, or C<sub>1-6</sub> haloalkyl;

15

and the pharmaceutically acceptable salts, and other pharmaceutically acceptable biohydrolyzable derivatives thereof, including esters, amides, carbamates, carbonates, ureides, solvates, hydrates, affinity reagents or prodrugs thereof.

20

For the avoidance of doubt when a group as defined above contains two or more radicals eg the radical R<sup>21</sup> as for example in the groups SO<sub>2</sub>NR<sup>21</sup>R<sup>21</sup> and NR<sup>3</sup>COR<sup>3</sup>, the two or more radicals i.e. R<sup>21</sup> may be the same or different.

25 For the purposes of this invention, alkyl relates to both straight chain and branched alkyl radicals of 1 to 12 carbon atoms, preferably 1 to 8 carbon atoms and most preferably 1 to 4 carbon atoms including but not limited to methyl, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl, isobutyl, tert-butyl n-pentyl, n-hexyl, n-heptyl, n-octyl. In particular, alkyl relates to a group having 1, 2, 3, 4,

5, 6, 7, 8, 9, 10, 11 or 12 carbon atoms. The term alkyl also encompasses cycloalkyl radicals including but not limited to cyclopropyl, cyclobutyl, CH<sub>2</sub>-cyclopropyl, CH<sub>2</sub>-cyclobutyl, cyclopentyl or cyclohexyl. In particular, cycloalkyl relates to a group having 3, 4, 5, 6, 7, 8, 9, 10, 11 or 12 carbon

5 atoms. Cycloalkyl groups may be optionally substituted or fused to one or more carbocyclyl or heterocyclyl group. Haloalkyl relates to an alkyl radical as defined above preferably having 1 to 8 carbon atoms, preferably 1 to 4 carbon atoms substituted with one or more halide atoms for example one or more of F, Cl, Br or I, such as CH<sub>2</sub>CH<sub>2</sub>Br, CF<sub>3</sub> or CCl<sub>3</sub>.

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The term "alkenyl" means a straight chain or branched alkenyl radical of 2 to 12 carbon atoms, preferably 2 to 6 carbon atoms and most preferably 2 to 4 carbon atoms, and containing one or more carbon-carbon double bonds and includes but is not limited to ethylene, n-propyl-1-ene, n-propyl-2-ene, 15 isopropylene, etc. In particular, alkenyl relates to a group having 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 or 12 carbon atoms. The term "alkynyl" means a straight chain or branched alkynyl radical of 2 to 12 carbon atoms, preferably 2 to 6 carbon atoms and most preferably 2 to 4 carbon atoms, and containing one or more carbon-carbon triple bonds and includes but is not limited to ethynyl, 2- 20 methylethynyl etc. In particular, alkynyl relates to a group having 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 or 12 carbon atoms.

"Carbocyclyl" relates to a saturated, partly unsaturated or unsaturated 3-12 membered hydrocarbon ring preferably a 6-12 membered hydrocarbon ring, 25 including cycloalkyl and aryl.

"Aryl" means an aromatic 3-12 membered hydrocarbon preferably a 6-12 membered hydrocarbon containing one ring or being fused to one or more

saturated or unsaturated rings including but not limited to phenyl, napthyl, anthracenyl or phenanthracenyl.

“Heteroaryl” means an aromatic 3-12 membered aryl preferably a 6-12 membered aryl containing one or more heteroatoms selected from N, O or S and containing one ring or being fused to one or more saturated or unsaturated rings and;

“Heterocyclyl” means a 3-12 membered ring system preferably a 6-12 membered ring system containing one or more heteroatoms selected from N, O or S and includes heteroaryl. In particular the terms “carbocyclyl”, “aryl”, “heteroaryl” and “heterocyclyl” relate to a group having 3, 4, 5, 6, 7, 8, 9, 10, 11 or 12 carbon atoms.

15 The heterocyclyl system can contain one ring or may be fused to one or more saturated or unsaturated rings; the heterocyclyl can be fully saturated, partially saturated or unsaturated and includes but is not limited to heteroaryl and heterocarbocyclyl. Examples of carbocyclyl or heterocyclyl groups include but are not limited to cyclohexyl, phenyl, acridine, benzimidazole, benzofuran, 20 benzothiophene, benzoxazole, benzothiazole, carbazole, cinnoline, dioxin, dioxane, dioxolane, dithiane, dithiazine, dithiazole, dithiolane, furan, imidazole, imidazoline, imidazolidine, indole, indoline, indolizine, indazole, isoindole, isoquinoline, isoxazole, isothiazole, morpholine, napthyridine, oxazole, oxadiazole, oxathiazole, oxathiazolidine, oxazine, oxadiazine, phenazine, 25 phenothiazine, phenoxazine, phthalazine, piperazine, piperidine, pteridine, purine, pyran, pyrazine, pyrazole, pyrazoline, pyrazolidine, pyridazine, pyridine, pyrimidine, pyrrole, pyrrolidine, pyrrolidine, quinoline, quinoxaline, quinazoline, quinolizine, tetrahydrofuran, tetrazine, tetrazole, thiophene,

thiadiazine, thiadiazole, thiatriazole, thiazine, thiazole, thiomorpholine, thianaphthalene, thiopyran, triazine, triazole, and trithiane.

For the purpose of the present invention, the term "fused" includes a polycyclic 5 compound in which one ring contains one or more atoms preferably one, two or three atoms in common with one or more other ring.

Halogen means F, Cl, Br or I, preferably F.

10 R<sup>1</sup> is preferably a group of formula (II) or an optionally substituted five or six membered carbocyclyl or heterocyclyl group wherein the carbocyclyl or heterocyclyl group is optionally fused to one or more unsaturated rings.

When R<sup>1</sup> is a substituted five or six membered carbocyclyl or heterocyclyl 15 group it is preferably selected from optionally substituted phenyl, acridine, benzimidazole, benzofuran, benzothiophene, benzoxazole, benzothiazole, cyclohexyl furan, imidazole, indole, isoindole, isoquinoline, isoxazole, isothiazole, morpholine, naphthaline, oxazole, phenazine, phenothiazine, phenoxazine, piperazine, piperidine, pyrazole, pyridazine, pyridine, pyrrole, 20 quinoline, quinolizine, tetrahydrofuran, tetrazine, tetrazole, thiophene, thiazole, thiomorpholine, thianaphthalene, thiopyran, triazine, triazole or trithiane.

When R<sup>1</sup> is a group of formula (II), X is preferably a group NR<sup>3</sup>, Y is 25 preferably absent and one or more of R<sup>2</sup> and R<sup>3</sup> are preferably hydrogen alkyl or cycloalkyl, in particular, the group of formula (II) is preferably an alkylamino or cycloalkylamino group preferably selected from optionally substituted methylamino, ethylamino, propylamino, isopropylamino, butylamino, cyclobutylamino, pentylamino, cyclopentylamino, hexylamino, cyclohexylamino, heptylamino, cycloheptylamino, octylamino and

cyclooctylamino. In particular, X is an alkylamino or a cycloalkylamino group wherein the alkyl group has 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 or 12 carbon atoms and the cycloalkyl group has 3, 4, 5, 6, 7, 8, 9, 10, 11 or 12 carbon atoms. R<sup>1</sup> may additionally be a group of formula (II) wherein X is NR<sup>3</sup> and R<sup>2</sup> and R<sup>3</sup> 5 form a 5, 6, 7 or 8 membered ring, said ring being partially, saturated, fully saturated or unsaturated and optionally substituted as previously discussed.

As discussed above, R<sup>1</sup> can be optionally substituted at any position on the alkylamino, cycloalkyl amino, carbocyclyl, heterocyclyl or optional fused ring.

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R<sup>1</sup> is preferably substituted with one or more of OR<sup>24</sup>, halogen, C<sub>1-6</sub> alkyl, C<sub>2-6</sub> alkenyl, C<sub>2-6</sub> alkynyl, C<sub>1-6</sub> haloalkyl, C<sub>1-6</sub>alkylaryl, C<sub>1-6</sub>alkylheterocyclyl, (CH<sub>2</sub>)<sub>n</sub>OR<sup>24</sup>, (CH<sub>2</sub>)<sub>n</sub>NR<sup>24</sup><sub>2</sub>, SR<sup>24</sup>, NO<sub>2</sub>, CN, NR<sup>24</sup><sub>2</sub>, CO<sub>2</sub>R<sup>24</sup>, NR<sup>24</sup>C(O)R<sup>24</sup>, NR<sup>24</sup>S(O)<sub>2</sub>R<sup>24</sup>, COR<sup>24</sup>, CONR<sup>24</sup><sub>2</sub>, S(O)<sub>2</sub>R<sup>24</sup>, S(O)R<sup>24</sup> or SO<sub>2</sub>NR<sup>24</sup><sub>2</sub>; 15 wherein R<sup>24</sup> is hydrogen, C<sub>1-4</sub> alkyl or C<sub>6-12</sub> aryl preferably phenyl, or C<sub>5-12</sub> heterocyclyl preferably pyridine, and n is 1, 2, 3, 4, 5 or 6.

wherein two R<sup>24</sup> in NR<sup>24</sup><sub>2</sub> may optionally form a partially saturated, unsaturated or fully saturated three to seven membered ring containing one to three 20 heteroatoms, said ring is preferably independently substituted with one or more of halogen, C<sub>1-12</sub> alkyl, C<sub>2-12</sub> alkenyl, C<sub>2-12</sub> alkynyl, C<sub>1-12</sub> haloalkyl, C<sub>3-12</sub> carbocyclyl, C<sub>3-12</sub> heterocyclyl, OR<sup>25</sup>, SR<sup>25</sup>, NO<sub>2</sub>, CN, NR<sup>25</sup><sub>2</sub>, NR<sup>25</sup>COR<sup>25</sup>, NR<sup>25</sup>CONR<sup>25</sup><sub>2</sub>, NR<sup>25</sup>COR<sup>25</sup>, NR<sup>25</sup>CO<sub>2</sub>R<sup>25</sup>, CO<sub>2</sub>R<sup>25</sup>, COR<sup>25</sup>, CONR<sup>25</sup><sub>2</sub>, S(O)<sub>2</sub>R<sup>25</sup>, SONR<sup>25</sup><sub>2</sub>, S(O)R<sup>25</sup>, SO<sub>2</sub>NR<sup>25</sup><sub>2</sub>, or NR<sup>25</sup>S(O)<sub>2</sub>R<sup>25</sup>; and each saturated carbon in 25 the optional ring is further optionally and independently substituted by =O, =S, NNR<sup>26</sup><sub>2</sub>, =N-OR<sup>26</sup>, =NNR<sup>26</sup>COR<sup>26</sup>, =NNR<sup>26</sup>CO<sub>2</sub>R<sup>26</sup>, =NNSO<sub>2</sub>R<sup>26</sup>, or =NR<sup>26</sup>; and each substitutable nitrogen atom is optionally substituted by R<sup>27</sup>, COR<sup>27</sup>, SO<sub>2</sub>R<sup>27</sup> or CO<sub>2</sub>R<sup>27</sup>;

wherein  $R^{25}$  is hydrogen,  $C_{1-12}$  alkyl,  $C_{6-12}$  carbocyclyl or  $C_{5-12}$  heterocyclyl, optionally substituted by one or more of  $C_{1-6}$  alkyl, halogen,  $C_{1-6}$  haloalkyl,  $OR^{28}$ ,  $SR^{28}$ ,  $NO_2$ ,  $CN$ ,  $NR^{28}R^{28}$ ,  $NR^{28}COR^{28}$ ,  $NR^{28}CONR^{28}R^{28}$ ,  $NR^{28}COR^{28}$ ,  $NR^{28}CO_2R^{28}$ ,  $CO_2R^{28}$ ,  $COR^{28}$ ,  $CONR^{28}R^{28}$ ,  $S(O)_2R^{28}$ ,  $SONR^{28}R^{28}$ ,  $S(O)R^{28}$ ,  
5  $SO_2NR^{28}R^{28}$ ,  $NR^{28}S(O)_2R^{28}$ , wherein the  $C_{1-12}$  alkyl group optionally incorporates one or two insertions selected from the group consisting of -O-, - $N(R^{28})$ -, -S(O)- and -S(O<sub>2</sub>)-, wherein each  $R^{28}$  may be the same or different and is as defined below;

10 wherein  $R^{26}$  is hydrogen,  $C_{1-12}$  alkyl,  $C_{6-12}$  carbocyclyl or  $C_{5-12}$  heterocyclyl, optionally substituted by one or more of  $C_{1-6}$  alkyl, halogen,  $C_{1-6}$  haloalkyl,  $OR^{28}$ ,  $SR^{28}$ ,  $NO_2$ ,  $CN$ ,  $NR^{28}R^{28}$ ,  $NR^{28}COR^{28}$ ,  $NR^{28}CONR^{28}R^{28}$ ,  $NR^{28}COR^{28}$ ,  $NR^{28}CO_2R^{28}$ ,  $CO_2R^{28}$ ,  $COR^{28}$ ,  $CONR^{28}R^{28}$ ,  $S(O)_2R^{28}$ ,  $S(O)R^{28}$ ,  $SO_2NR^{28}R^{28}$ ,  $NR^{28}S(O)_2R^{28}$ , wherein the  $C_{1-12}$  alkyl group optionally incorporates one or two  
15 insertions selected from the group consisting of -O-, - $N(R^{28})$ -, -S(O)- and -S(O<sub>2</sub>)-, wherein each  $R^{28}$  may be the same or different and is as defined below;

wherein  $R^{27}$  is hydrogen,  $C_{1-6}$  alkyl,  $C_{1-6}$  haloalkyl or  $C_{6-12}$  aryl;

20 wherein  $R^{28}$  is hydrogen,  $C_{1-6}$  alkyl, or  $C_{1-6}$  haloalkyl.

$R^4$  is preferably selected from phenyl, cyclohexyl, acridine, benzimidazole, benzofuran, benzothiophene, benzoxazole, benzothiazole, indole, isoindole, indolizine, indazole, isoindole, isoquinoline, morpholine, napthalene, 25 phenazine, phenothiazine, phenoxazine, piperazine, piperidine, pyridazine, pyridine, pyridinyl, pyrimidinyl, pyrazinyl, pyridazinyl, quinoline, quinolizine, tetrazine, thiomorpholine, thianaphthalene, thiopyran, triazine, trithiane, furan, imidazole, isoxazole, isothiazole, oxazole, oxadiazole, oxathiazole, pyrazole, pyrrole, tetrazole, thiophene, thiadiazole, thiatriazole, thiazole or triazole.

As discussed above,  $R^4$  can be optionally substituted at any position on the carbocyclyl, heterocyclyl or optional fused ring. Preferably, each substitutable carbon or hetero-atom in  $R^4$  is optionally and independently substituted by one or more of  $C_{1-6}$  alkyl,  $OR^{20}$ ,  $SR^{20}$ ,  $NO_2$ ,  $CN$ ,  $NR^{20}_2$ ,  $NR^{20}COR^{20}$ ,  $NR^{20}CONR^{20}_2$ ,  $NR^{20}COR^{20}$ ,  $NHCO_2R^{20}$ ,  $CO_2R^{20}$ ,  $COR^{20}$ ,  $CONR^{20}_2$ ,  $S(O)_2R^{20}$ ,  $SONR^{20}_2$ ,  $S(O)R^{20}$ ,  $SO_2NR^{20}_2$ , or  $NR^{20}S(O)_2R^{20}$ ;

wherein  $R^{20}$  is hydrogen,  $C_{1-6}$  alkyl, or  $C_{1-6}$  haloalkyl.

10

When  $R^4$  is a six-membered carbocyclyl or heterocyclyl group,  $R^4$  is preferably substituted with one or more of  $OR^{29}$ ,  $NR^{29}_2$ ,  $SR^{29}$ ,  $(CH_2)_nOR^{29}$ ,  $(CH_2)_nNR^{29}_2$ , halogen,  $C_{1-6}$  alkyl,  $C_{2-6}$  alkenyl,  $C_{2-6}$  alkynyl, haloalkyl,  $NO_2$ ,  $CN$ ,  $NR^{29}C(O)R^{29}$ ,  $NR^{29}S(O)_2R^{29}$ ,  $CO_2R^{29}$ ,  $COR^{29}$ ,  $CONR^{29}_2$ ,  $S(O)_2R^{29}$ ,  $S(O)R^{29}$  or  $SO_2NR^{29}_2$ ;

wherein  $R^{29}$  is hydrogen,  $C_{1-4}$  alkyl,  $C_{5-12}$  heterocyclyl or  $C_{6-12}$  aryl preferably phenyl, and  $n$  is 1, 2, 3, 4, 5 or 6.

wherein two  $R^{29}$  in  $NR^{29}_2$  may optionally form a partially saturated, unsaturated or fully saturated five to seven membered ring containing one to three heteroatoms, optionally and independently substituted with one or more of halogen,  $C_{1-12}$  alkyl,  $C_{2-12}$  alkenyl,  $C_{2-12}$  alkynyl,  $C_{1-12}$  haloalkyl,  $C_{6-12}$  carbocyclyl,  $C_{5-12}$  heterocyclyl,  $OR^{30}$ ,  $SR^{30}$ ,  $NO_2$ ,  $CN$ ,  $NR^{30}_2$ ,  $NR^{30}COR^{30}$ ,  $NR^{30}CONR^{30}_2$ ,  $NR^{30}COR^{30}$ ,  $NR^{30}CO_2R^{30}$ ,  $CO_2R^{30}$ ,  $COR^{30}$ ,  $CONR^{30}_2$ ,  $S(O)_2R^{30}$ ,  $SONR^{30}_2$ ,  $S(O)R^{30}$ ,  $SO_2NR^{30}_2$ , or  $NR^{30}S(O)_2R^{30}$ ; and each saturated carbon in the optional ring is further optionally and independently substituted by  $=O$ ,  $=S$ ,  $NNR^{31}_2$ ,  $=N-OR^{31}$ ,  $=NNR^{31}COR^{31}$ ,  $=NNR^{31}CO_2R^{31}$ ,  $=NNSO_2R^{31}$ , or  $=NR^{31}$ ; and each substitutable nitrogen atom is optionally substituted by  $R^{32}$ ,  $COR^{32}$ ,  $SO_2R^{32}$  or  $CO_2R^{32}$ ;

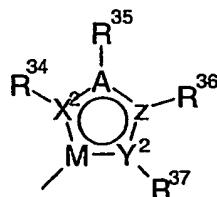
wherein  $R^{30}$  is hydrogen,  $C_{1-12}$  alkyl,  $C_{6-12}$  carbocyclyl or  $C_{5-12}$  heterocyclyl, optionally substituted by one or more of  $C_{1-6}$  alkyl, halogen,  $C_{1-6}$  haloalkyl,  $OR^{33}$ ,  $SR^{33}$ ,  $NO_2$ ,  $CN$ ,  $NR^{33}R^{33}$ ,  $NR^{33}COR^{33}$ ,  $NR^{33}CONR^{33}R^{33}$ ,  $NR^{33}COR^{33}$ ,  $NR^{33}CO_2R^{33}$ ,  $CO_2R^{33}$ ,  $COR^{33}$ ,  $CONR^{33}R^{33}$ ,  $S(O)_2R^{33}$ ,  $SONR^{33}R^{33}$ ,  $S(O)R^{33}$ , 5  $SO_2NR^{33}R^{33}$ ,  $NR^{33}S(O)_2R^{33}$ , wherein the  $C_{1-12}$  alkyl group optionally incorporates one or two insertions selected from the group consisting of -O-, -N( $R^{33}$ )-, -S(O)- and -S(O<sub>2</sub>)-, wherein each  $R^{33}$  may be the same or different and is as defined below;

10 wherein  $R^{31}$  is hydrogen,  $C_{1-12}$  alkyl,  $C_{6-12}$  carbocyclyl or  $C_{5-12}$  heterocyclyl, optionally substituted by one or more of  $C_{1-6}$  alkyl, halogen,  $C_{1-6}$  haloalkyl,  $OR^{33}$ ,  $SR^{33}$ ,  $NO_2$ ,  $CN$ ,  $NR^{33}R^{33}$ ,  $NR^{33}COR^{33}$ ,  $NR^{33}CONR^{33}R^{33}$ ,  $NR^{33}COR^{33}$ ,  $NR^{33}CO_2R^{33}$ ,  $CO_2R^{33}$ ,  $COR^{33}$ ,  $CONR^{33}R^{33}$ ,  $S(O)_2R^{33}$ ,  $S(O)R^{33}$ ,  $SO_2NR^{33}R^{33}$ ,  $NR^{33}S(O)_2R^{33}$ , wherein the  $C_{1-12}$  alkyl group optionally incorporates one or two 15 insertions selected from the group consisting of -O-, -N( $R^{33}$ )-, -S(O)- and -S(O<sub>2</sub>)-, wherein each  $R^{21}$  may be the same or different and is as defined below;

wherein  $R^{32}$  is hydrogen,  $C_{6-12}$  aryl,  $C_{1-6}$  alkyl or  $C_{1-6}$  haloalkyl;

20 wherein  $R^{33}$  is hydrogen,  $C_{1-6}$  alkyl, or  $C_{1-6}$  haloalkyl.

When  $R^4$  is a five-membered heterocyclyl, it is preferably a group



Wherein A, X<sup>2</sup>, Y<sup>2</sup> or Z are independently selected from N, O, C, S and M is C or N, wherein one, two, three or four of A, X<sup>2</sup>, Y<sup>2</sup>, Z and M is other than C, preferably R<sup>4</sup> is furan, imidazole, isoxazole, isothiazole, oxazole, oxadiazole, oxatriazole, pyrazole, pyrrole, tetrazole, thiophene, thiadiazole, thiatriazole, 5 thiazole or triazole;

R<sup>34</sup>, R<sup>35</sup>, R<sup>36</sup> or R<sup>37</sup> are independently selected from a lone electron pair, hydrogen, halogen, C<sub>1-12</sub> alkyl, C<sub>1-12</sub> haloalkyl, OR<sup>38</sup>, SR<sup>38</sup>, NO<sub>2</sub>, CN, NR<sup>38</sup><sub>2</sub>, NR<sup>38</sup>COR<sup>38</sup>, NR<sup>38</sup>CONR<sup>38</sup><sub>2</sub>, NR<sup>38</sup>COR<sup>38</sup>, NR<sup>38</sup>CO<sub>2</sub>R<sup>38</sup>, (CH<sub>2</sub>)<sub>n</sub>OR<sup>38</sup>, 10 (CH<sub>2</sub>)<sub>n</sub>NR<sup>38</sup><sub>2</sub>, CO<sub>2</sub>R<sup>38</sup>, COR<sup>38</sup>, CONR<sup>38</sup><sub>2</sub>, S(O)<sub>2</sub>R<sup>38</sup>, SONR<sup>38</sup><sub>2</sub>, S(O)R<sup>38</sup>, SO<sub>2</sub>NR<sup>38</sup><sub>2</sub>, or NHS(O)<sub>2</sub>R<sup>38</sup>;

wherein n is 1 to 6, preferably n is 1, 2 or 3;

or wherein any two of R<sup>34</sup>, R<sup>35</sup>, R<sup>36</sup> or R<sup>37</sup> may optionally form a partially 15 saturated, unsaturated or fully saturated five to seven membered ring containing zero to three heteroatoms, each saturated carbon in the optional fused ring is further optionally and independently substituted with one or more of halogen, C<sub>1-12</sub> alkyl, C<sub>2-12</sub> alkenyl, C<sub>2-12</sub> alkynyl, C<sub>1-12</sub> haloalkyl, C<sub>6-12</sub> carbocyclyl, C<sub>5-12</sub> heterocyclyl, OR<sup>38</sup>, SR<sup>38</sup>, NO<sub>2</sub>, CN, NR<sup>38</sup><sub>2</sub>, NR<sup>38</sup>CONR<sup>38</sup><sub>2</sub>, NR<sup>38</sup>COR<sup>38</sup>, 20 NR<sup>38</sup>CO<sub>2</sub>R<sup>38</sup>, (CH<sub>2</sub>)<sub>n</sub>OR<sup>38</sup>, (CH<sub>2</sub>)<sub>n</sub>NR<sup>38</sup><sub>2</sub>, CO<sub>2</sub>R<sup>38</sup>, COR<sup>38</sup>, CONR<sup>38</sup><sub>2</sub>, S(O)<sub>2</sub>R<sup>38</sup>, SONR<sup>38</sup><sub>2</sub>, S(O)R<sup>38</sup>, SO<sub>2</sub>NR<sup>38</sup><sub>2</sub>, or NR<sup>38</sup>S(O)<sub>2</sub>R<sup>38</sup>; and each saturated carbon in the optional fused ring is further optionally and independently substituted by =O, =S, NNR<sup>39</sup><sub>2</sub>, =N-OR<sup>39</sup>, =NNR<sup>39</sup>COR<sup>39</sup>, =NNR<sup>39</sup>CO<sub>2</sub>R<sup>39</sup>, =NNSO<sub>2</sub>R<sup>39</sup>, or =NR<sup>39</sup>; and each substitutable nitrogen atom in R<sup>4</sup> is optionally substituted by 25 R<sup>40</sup>, COR<sup>40</sup>, SO<sub>2</sub>R<sup>40</sup> or CO<sub>2</sub>R<sup>40</sup>;

wherein n is 1 to 6, preferably n is 1, 2 or 3;

wherein R<sup>38</sup> is hydrogen, C<sub>1-12</sub> alkyl, C<sub>6-12</sub> carbocyclyl or C<sub>5-12</sub> heterocyclyl, optionally substituted by one or more of C<sub>1-6</sub> alkyl, halogen, C<sub>1-6</sub> haloalkyl,

OR<sup>41</sup>, SR<sup>41</sup>, NO<sub>2</sub>, CN, NR<sup>41</sup>R<sup>41</sup>, NR<sup>41</sup>CONR<sup>41</sup>R<sup>41</sup>, NR<sup>41</sup>COR<sup>41</sup>, NR<sup>41</sup>CO<sub>2</sub>R<sup>41</sup>, CO<sub>2</sub>R<sup>41</sup>, COR<sup>41</sup>, CONR<sup>41</sup><sub>2</sub>, S(O)<sub>2</sub>R<sup>41</sup>, SONR<sup>41</sup><sub>2</sub>, S(O)R<sup>41</sup>, SO<sub>2</sub>NR<sup>41</sup>R<sup>41</sup>, NR<sup>41</sup>S(O)<sub>2</sub>R<sup>41</sup>, wherein the C<sub>1-12</sub> alkyl group optionally incorporates one or two insertions selected from the group consisting of -O-, -N(R<sup>41</sup>)-, -S(O)- and -S(O<sub>2</sub>)-, wherein each R<sup>41</sup> may be the same or different and is as defined below;

wherein R<sup>39</sup> is hydrogen, C<sub>1-12</sub> alkyl, carbocyclyl or heterocyclyl, optionally substituted by one or more of C<sub>1-6</sub> alkyl, halogen, C<sub>1-6</sub> haloalkyl, OR<sup>41</sup>, SR<sup>41</sup>, NO<sub>2</sub>, CN, NR<sup>41</sup>R<sup>41</sup>, NR<sup>41</sup>COR<sup>41</sup>, NR<sup>41</sup>CONR<sup>41</sup>R<sup>41</sup>, NR<sup>41</sup>COR<sup>41</sup>, NR<sup>41</sup>CO<sub>2</sub>R<sup>41</sup>, CO<sub>2</sub>R<sup>41</sup>, COR<sup>41</sup>, CONR<sup>41</sup><sub>2</sub>, S(O)<sub>2</sub>R<sup>41</sup>, S(O)R<sup>41</sup>, SO<sub>2</sub>NR<sup>41</sup>R<sup>41</sup>, NR<sup>41</sup>S(O)<sub>2</sub>R<sup>41</sup>, wherein the C<sub>1-12</sub> alkyl group optionally incorporates one or two insertions selected from the group consisting of -O-, -N(R<sup>41</sup>)-, -S(O)- and -S(O<sub>2</sub>)-, wherein each R<sup>41</sup> may be the same or different and is as defined below;

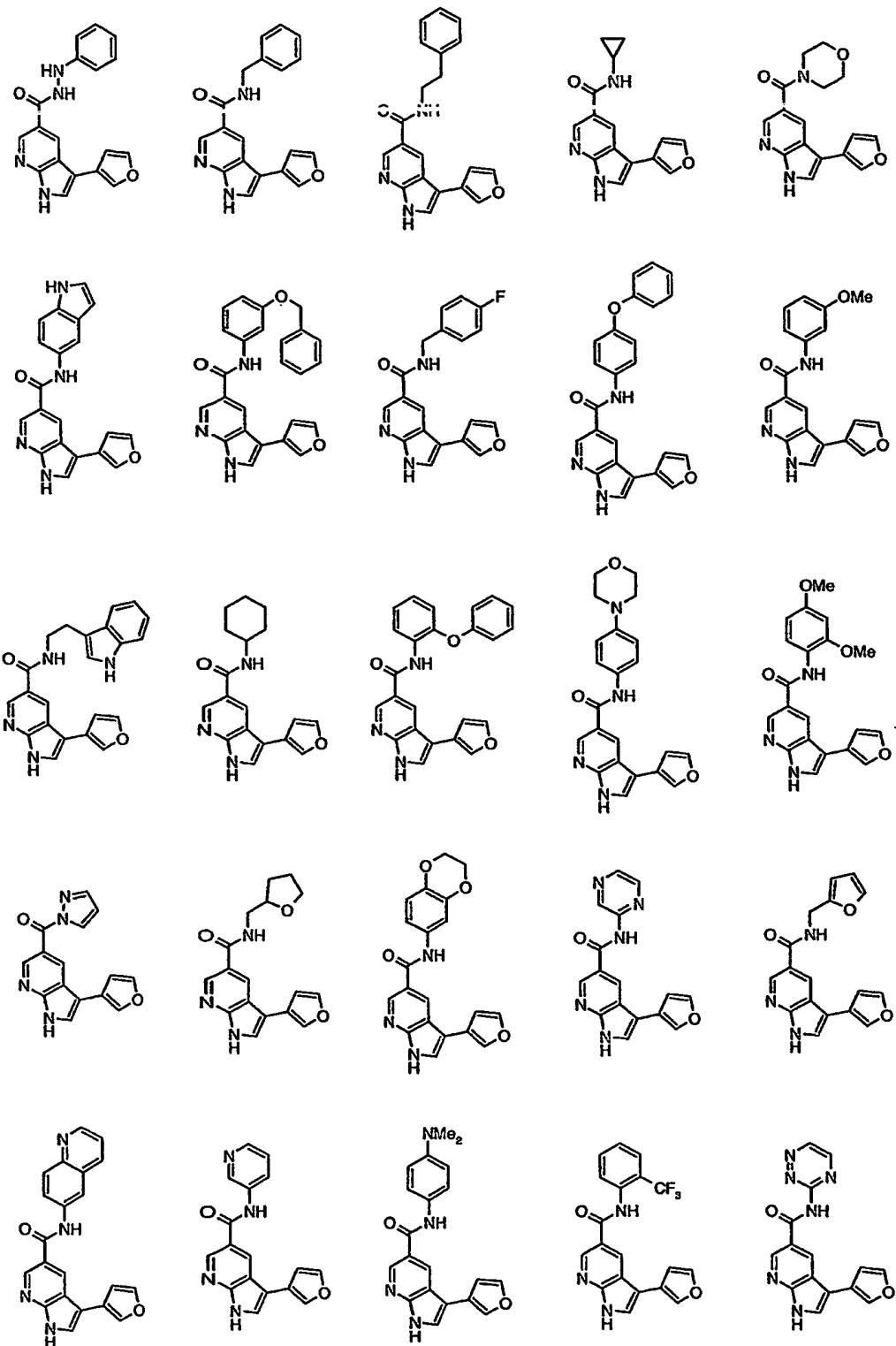
15 wherein R<sup>40</sup> is hydrogen, C<sub>1-6</sub> alkyl, C<sub>1-6</sub> haloalkyl or C<sub>6-12</sub> aryl.

wherein R<sup>41</sup> is hydrogen, C<sub>1-6</sub> alkyl, or C<sub>1-6</sub> haloalkyl.

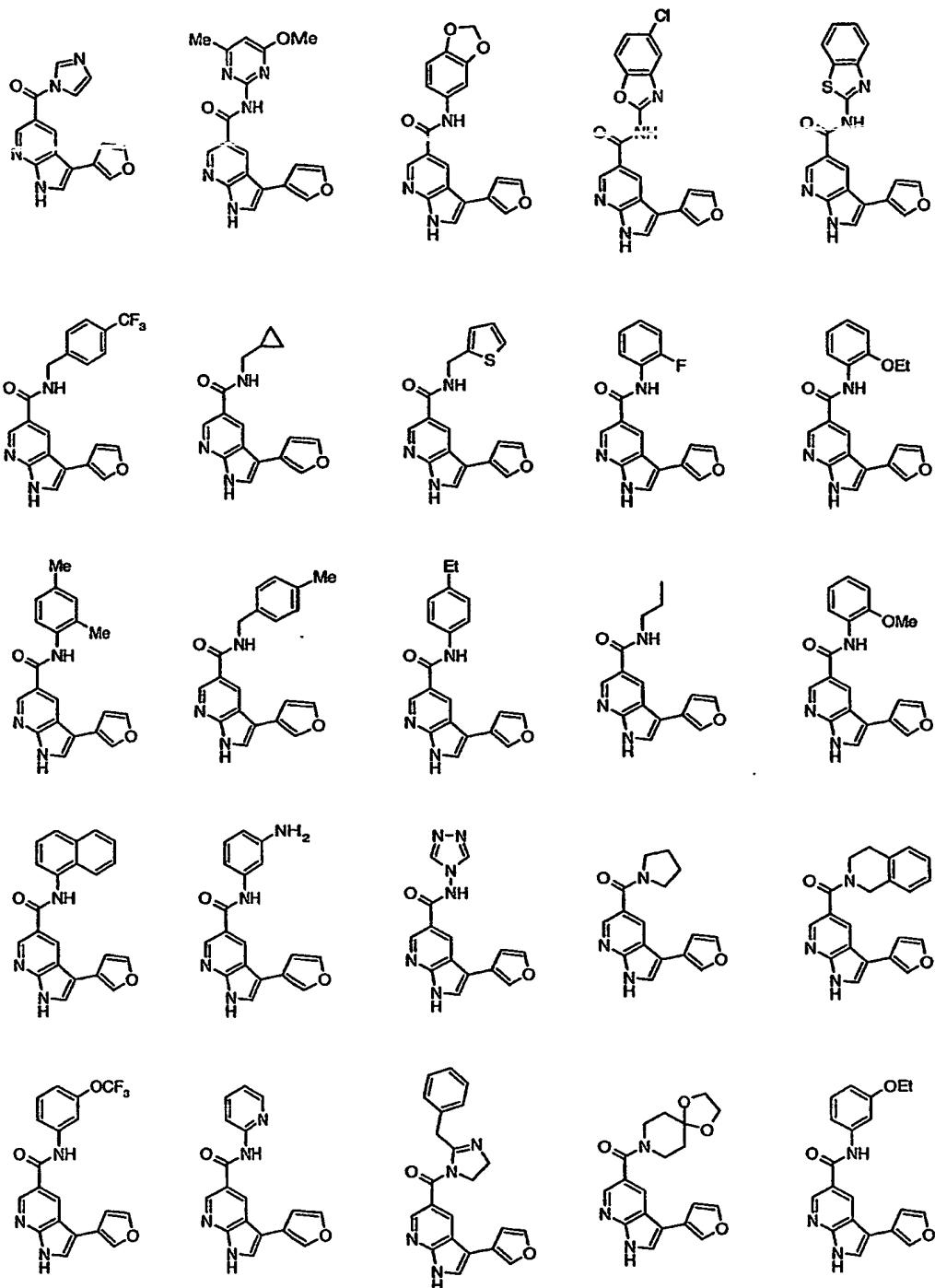
More preferably R<sup>34</sup>, R<sup>35</sup>, R<sup>36</sup> or R<sup>37</sup> are independently selected from a lone electron pair, hydrogen, halogen, C<sub>1-6</sub> alkyl, C<sub>1-6</sub> haloalkyl, OR<sup>42</sup>, SR<sup>42</sup>, CN, NR<sup>42</sup><sub>2</sub>, NR<sup>42</sup>COR<sup>42</sup>, CO<sub>2</sub>R<sup>42</sup>, COR<sup>42</sup>, CONR<sup>42</sup><sub>2</sub>, S(O)<sub>2</sub>R<sup>42</sup>, or S(O)R<sup>42</sup>; wherein R<sup>42</sup> is hydrogen, C<sub>1-4</sub> alkyl, preferably methyl or ethyl or carbocyclyl, preferably phenyl.

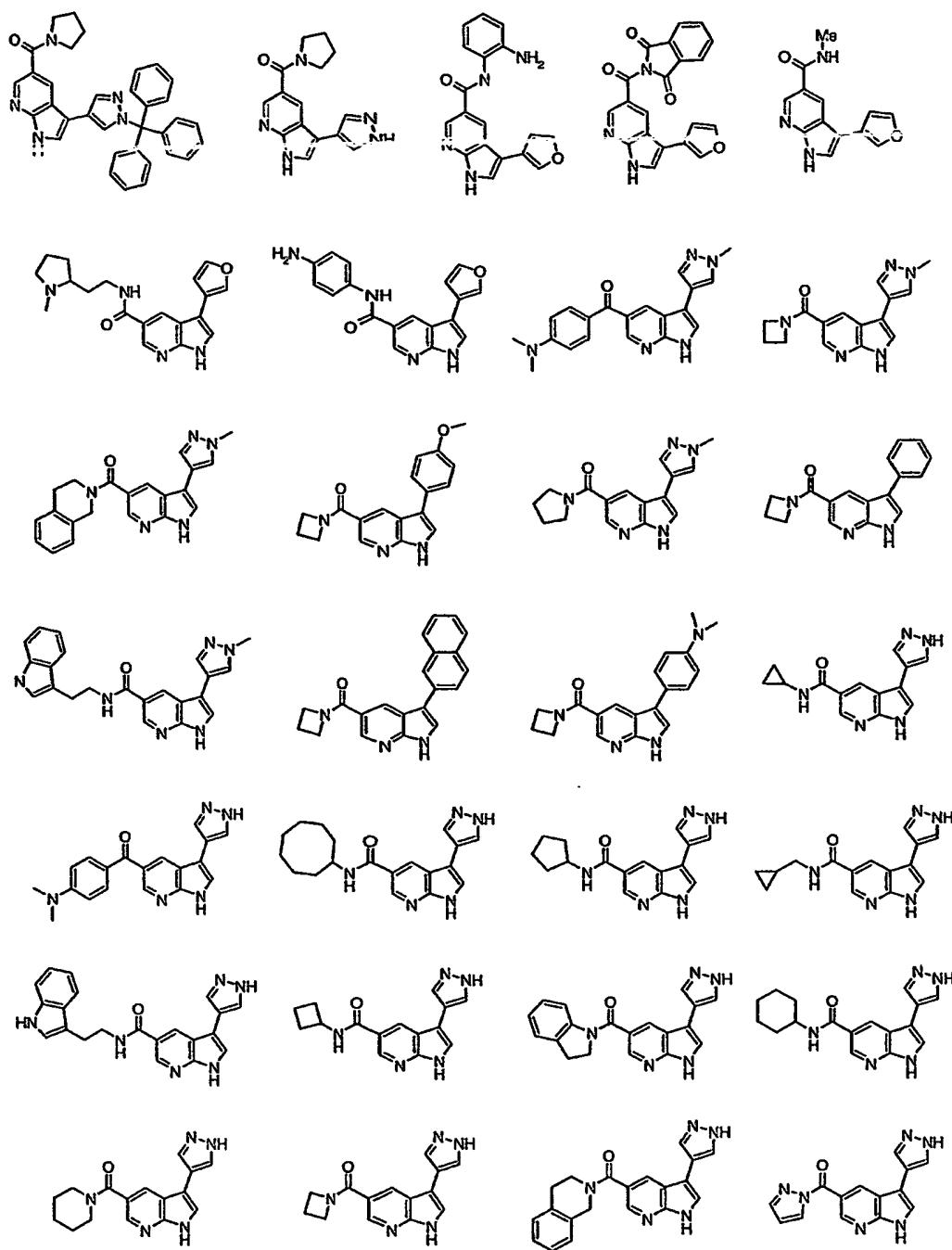
25 Representative compounds according to the first aspect of the invention are illustrated below.

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The compounds of the first aspect may be provided as a salt, preferably as a pharmaceutically acceptable salt of compounds of formula (I). Examples of 5 pharmaceutically acceptable salts of these compounds include those derived

from organic acids such as acetic acid, malic acid, tartaric acid, citric acid, lactic acid, oxalic acid, succinic acid, fumaric acid, maleic acid, benzoic acid, salicylic acid, phthalylacetic acid, maleic acid, methanesulphonic acid, benzenesulphonic acid and p-toluenesulphonic acid, mineral acids such as 5 hydrochloric and sulphuric acid and the like, giving methanesulphonate, benzenesulphonate, p-toluenesulphonate, hydrochloride and sulphate, and the like, respectively or those derived from bases such as organic and inorganic bases. Examples of suitable inorganic bases for the formation of salts of compounds for this invention include the hydroxides, carbonates, and 10 bicarbonates of ammonia, lithium, sodium, calcium, potassium, aluminium, iron, magnesium, zinc and the like. Salts can also be formed with suitable organic bases. Such bases suitable for the formation of pharmaceutically acceptable base addition salts with compounds of the present invention include organic bases, which are nontoxic and strong enough to form salts. Such 15 organic bases are already well known in the art and may include amino acids such as arginine and lysine, mono-, di-, or trihydroxyalkylamines such as mono-, di-, and triethanolamine, choline, mono-, di-, and trialkylamines, such as methylamine, dimethylamine, and trimethylamine, guanidine; N-methylglucosamine; N-methylpiperazine; morpholine; ethylenediamine; N- 20 benzylphenethylamine; tris(hydroxymethyl) aminomethane; and the like.

Salts may be prepared in a conventional manner using methods well known in the art. Acid addition salts of said basic compounds may be prepared by dissolving the free base compounds according to the first aspect of the 25 invention in aqueous or aqueous alcohol solution or other suitable solvents containing the required acid. Where a compound of the invention contains an acidic function, a base salt of said compound may be prepared by reacting said compound with a suitable base. The acid or base salt may separate directly or

can be obtained by concentrating the solution e.g. by evaporation. The compounds of this invention may also exist in solvated or hydrated forms.

The invention also extends to a prodrug of the aforementioned compounds such 5 as an ester or amide thereof. A prodrug is any compound that may be converted under physiological conditions or by solvolysis to any of the compounds of the invention or to a pharmaceutically acceptable salt of the compounds of the invention. A prodrug may be inactive when administered to a subject but is converted *in vivo* to an active compound of the invention.

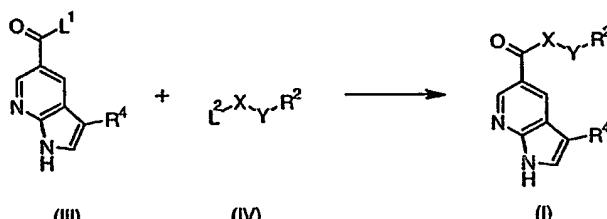
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The compounds of the invention may contain one or more asymmetric carbon atoms and may exist in racemic and optically active forms. The compounds of the invention may exist in trans or cis form. The first aspect of the invention covers all of these compounds.

15

The second aspect of the invention provides a process for the manufacture of a compound of formula (I) wherein R<sup>1</sup> is a group of formula (II) as defined in the first aspect of the invention comprising the condensation of an intermediate (III) with an intermediate (IV).

20



wherein R<sup>2</sup> and R<sup>4</sup> are as defined in the first aspect of the invention; L<sup>1</sup> and L<sup>2</sup> are independently a leaving group wherein L<sup>1</sup> and L<sup>2</sup> together form a condensation product.

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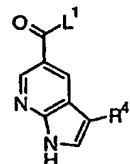
According to the process, a compound of the general formula (III), undergoes a condensation reaction with the compound of the general formula (IV), to form a compound of general formula I. In formulae (III) and (IV), L<sup>1</sup> and L<sup>2</sup> represent radicals that together form a condensation product, e.g. H and OH or H and Cl.

5 Preferably L<sup>1</sup> is OH, OR<sup>50</sup>, OM, Cl, Br or I wherein R<sup>50</sup> is C<sub>1-6</sub> alkyl, preferably methyl or ethyl and M is a metal, preferably Na, Li, K, Ca, Mg or Ba, and L<sup>2</sup> is preferably hydrogen or M. The condensation reaction occurs in a solution, preferably in a polar aprotic solvent such as e.g. dimethylformamide or dichloromethane. The condensation reaction may occur under the influence of

10 coupling agents such as, for instance WSCl, DCC, benzotriazole-1-yl-oxy-tris-(dimethylamino)-phosphonium hexafluorophosphate (BOP), PyBrOP, etc., and in the presence of a tertiary amine (e.g. triethylamine) and 1-hydroxybenzotriazole (HOBT). Alternatively, the acid (III) may be first converted to an acid chloride by treatment with, for example, oxalyl chloride or

15 thionyl chloride, and then without purification, reacted with, e.g. amines of formula (IV).

The third aspect of the invention provides a compound of formula (III)



(III)

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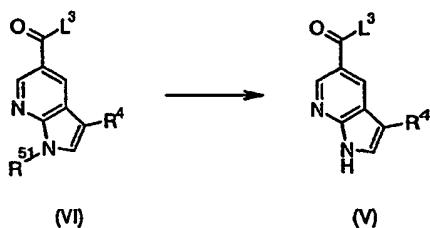
wherein R<sup>4</sup> is as defined in the first aspect of the invention and L<sup>1</sup> is OH, OR<sup>50</sup>, OM, Cl, Br, I; R<sup>50</sup> is C<sub>1-6</sub> alkyl, preferably methyl or ethyl; and M is metal, preferably Na, Li, K, Ca, Mg, Ba.

25

A compound of formula (III) may undergo one or more further reactions to

provide a different compound of formula (III). For example, a compound may undergo a hydrolysis, reduction, oxidation, elimination, substitution and/or addition reaction.

5 The fourth aspect of the invention provides a process for the manufacture of a compound of formula (V) comprising removal of group  $R^{51}$  from an intermediate (VI)



wherein  $L^3$  is  $R^1$  or  $L^1$ ,

10 wherein  $R^1$  is as defined in the first aspect and  
 $L^1$  is as defined in the second or third aspect;  
 $R^4$  is as defined in the first aspect, and  
 $R^{51}$  is an amino protecting group. The pyrrole nitrogen can be protected using  
any protection known in the art.  $R^{51}$  can therefore include  $R^{52}SO_2$ ,  $R^{52}C(O)$ ,

15  $R^{52}_3Si$ ,  $R^{52}OCH_2$ ,  $(R^{52})_2NSO_2$ ,  $(R^{52})_2NC(O)$ ,  $R^{52}OC(O)$ ,  $R^{52}(R^{52}O)CH$ ,  
 $R^{52}CH_2CH_2$ ,  $R^{52}CH_2$ ,  $PhC(O)CH_2$ ,  $CH_2=CH$ ,  $ClCH_2CH_2$ ,  $Ph_3C$ ,  $Ph_2(4$ -  
pyridyl)C,  $Me_2N$ ,  $HO-CH_2$ ,  $R^{52}OCH_2$ ,  $(R^{52})_3SiOCH_2$ ,  $(R^{52}O)_2CH$ , t-  
 $BuOC(O)CH_2$ ,  $Me_2NCH_2$ , and tetrahydropyranylamine,  
wherein  $R^{52}$  is  $C_{1-6}$  alkyl or  $C_{6-12}$  aryl.

20

More preferably  $R^{51}$  is sulfonamide, most preferably benzenesulfonamide,  $(R^{52})_2NSO_2$ , and  $(R^{52})_2NC(O)$ ,

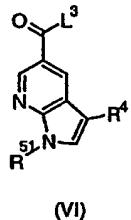
Removal of the protecting group can be afforded using conditions relevant to  
the protecting group used i.e. sulfonamide or amide protection can be removed  
by hydrolysis under basic conditions for example sodium hydroxide in water-

ethanol, and silyl protection can be removed under acidic conditions for example TFA, HCl or using a source of fluoride, for example TB AF.

It will be appreciated that when  $L^3$  is  $R^1$  the deprotection will afford directly the 5 compound of formula (I).

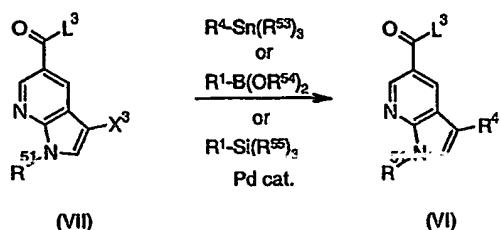
It will be further appreciated that when  $L^1$  is  $OR^{50}$  the hydrolytic removal of 10  $R^{51}$  under basic conditions is accompanied by hydrolysis of the ester functionality to afford compound (III) where  $L^1$  is  $OM$ , or  $OH$  after acidification of the reaction mixture.

The fifth aspect of the invention provides a compound of formula (VI)



wherein  $R^4$  is as defined in the first aspect,  
15  $L^3$  is as defined in the fourth aspect; and  
 $R^{51}$  is an amino protecting group as defined in the fourth aspect.

The sixth aspect of the invention provides a process for the manufacture of a compound of formula (VI) as defined in the fifth aspect of the invention  
20 comprising a a) reaction of a compound of formula (VII) with stannane  $R^4-Sn(R^{53})_3$  in the presence of a palladium catalyst or b) reaction of a compound of formula (VII) with boronic acid or ester  $R^4-B(OR^{54})_2$  in a presence of a suitable palladium catalyst or c) reaction of a compound of formula (VII) with silane  $R^4-Si(R^{55})_3$  in the presence of a palladium catalyst;



wherein  $R^4$  is as defined in the first aspect,

$L^3$  is as defined in the fourth aspect.

$R^{51}$  is an amino protecting group defined in the fourth aspect.

5  $X^3$  is F, Cl, Br I or  $CF_3SO_3$  preferably I or Br,

and wherein R<sup>53</sup> is independently C<sub>1-6</sub> alkyl;

$R^{54}$  is independently hydrogen or  $C_{1-6}$  alkyl or wherein two  $R^{54}$  groups together optionally form a five, six or seven membered ring with the boron and oxygen

10 atoms, wherein the ring is optionally substituted with one or more  $C_{1-6}$  alkyl group. Preferably,  $R^{54}$  is hydrogen or both  $R^{54}$  groups form the group —  
 $C(CH_3)_2-C(CH_3)_2-$ ;

and R<sup>55</sup> is independently C<sub>1-6</sub> alkyl, F, OH.

15 Suitable catalysts for the purpose of this invention include  $(PPh_3)_2PdCl_2$ ,  $(PPh_3)_4Pd$ ,  $Pd(OAc)_2$ ,  $[PdCl(\eta^3-C_3H_5)_2]$ ,  $Pd_2(dbu)_3$ ,  $Pd(dbu)_2$  ( $dbu =$  dibenzylidenacetone) and/or  $Pd/P(t-Bu)_3$ .

It will be appreciated that the reaction set out as option a) for the sixth aspect is a Stille reaction, which can be carried out according to Stille *Angew. Chem., Int. ed. Engl.* 1986, 25, 508; Mitchell *Synthesis*, 1992, 803, or Little *et al. J. Am. Chem. Soc.* 2002, 124, 6343.

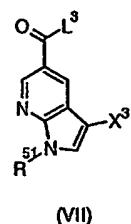
The reaction set out as option b) for the sixth aspect is a Suzuki reaction which  
25 can be carried out according to Suzuki Pure Appl. Chem. 1991, 63, 419 or  
Littke J. Am. Chem. Soc. 2000, 122, 4020

It will be appreciated that the reaction set out as option c) for the sixth aspect is a Hiyama reaction which can be carried out according to Hatanaka et al. *J. Org. Chem.* 1988, 53, 918, Hatanaka et al. *Synlett*, 1991, 845, Tamao et al.

5 Tetrahedron Lett. 1989, 30, 6051 or Denmark et al. Org. Lett. 2000, 2, 565, ibid. 2491.

It will further be appreciated that when  $R^{51}$  is replaced with hydrogen the process of the sixth aspect yields a compound of formula (III) as defined in the 10 fourth aspect of the invention.

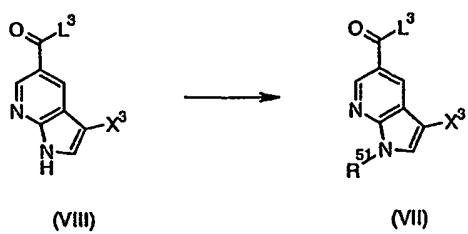
The seventh aspect of the invention provides a compound of formula (VII)



wherein  $L^3$  is as defined in the fourth aspect;

15 R<sup>51</sup> is an amino protecting group as defined in the fourth aspect; and X<sup>3</sup> is as defined in the sixth aspect.

The eighth aspect of the invention provides a process for the manufacture of a compound of formula (VII) comprising protection of the pyrrole nitrogen of a compound of formula (VIII).



wherein  $L^3$  is as defined in the fourth aspect;

$R^{51}$  is an amino protecting group defined in the fourth aspect, and

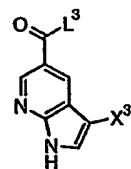
$X^3$  is as defined in the sixth aspect

5 Conditions for the introduction of the protecting group  $R^{51}$  will depend upon the protecting group used. Compound (VII) can be produced by the initial formation of the relevant salt, for example by treatment with BuLi in THF or NaH in DMF, followed by reaction of the salt with an electrophile such as sulfonyl halide, or acid chloride. Alternatively a compound of formula (VII)

10 10 can be produced by the direct reaction of compound (VIII) with an electrophile such as benzenesulfonyl halide, preferably benzenesulfonyl chloride. This reaction is preferably carried out in the presence of base (such as sodium hydroxide) and a phase transfer catalyst such as tetra-n-butylammonium bromide or tetra-n-butylammonium hydrogen sulphate.

15

The ninth aspect of the invention provides a compound of formula (VIII)



(VIII)

wherein  $L^3$  is as defined in the fourth aspect and

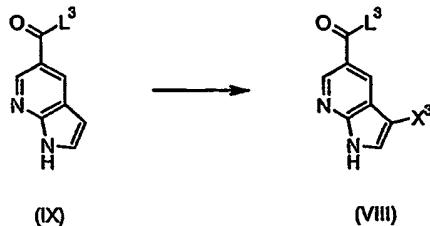
$X^3$  is as defined in the sixth aspect.

20

The tenth aspect of the invention provides a process for the production of a compound of formula (VIII) by the introduction of an  $X^3$  group into a compound of formula (IX). Compound (VIII) can be produced from compound (IX) by halogenation under anhydrous conditions or by reaction with ICl under basic conditions (such as pyridine or i-Pr<sub>2</sub>NEt in a chlorinated solvent such as CH<sub>2</sub>Cl<sub>2</sub>, CHCl<sub>3</sub>, CCl<sub>4</sub>) or NBS in an anhydrous solvent such as CH<sub>2</sub>Cl<sub>2</sub>, CHCl<sub>3</sub>,

25

$\text{CCl}_4$ ). Where  $\text{X}^3$  is iodine, it may preferably be introduced by direct action of  $\text{I}_2$  on (IX) in the presence of a strong base such as sodium hydroxide or potassium hydroxide in anhydrous solvent such as dimethylformamide.

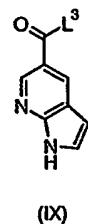


5 wherein  $L^3$  is as defined in the fourth aspect and  $X^3$  is as defined in the sixth aspect.

Preparation of compound of general formula (IX) wherein  $L^3$  is carbocyclyl or heterocyclyl has been disclosed in GB0305142.2.

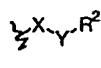
10

The eleventh aspect of the invention provides compound of formula (IX)



15 wherein  $L^3$  is as defined in the fourth aspect with the exception that  $L^3$  is not carbocyclyl or heterocyclyl;

in particular wherein  $L^3$  is a group  $L^1$  as defined in the second aspect or a group  $R^1$ , wherein  $R^1$  is a group of formula (II)



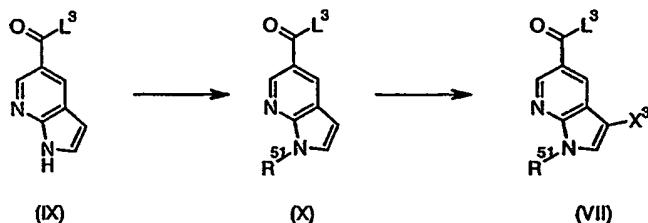
20

wherein X is NR<sup>3</sup>, O, S or (CR<sup>22</sup>R<sup>22</sup>)<sub>n</sub>, Y is absent or is NR<sup>23</sup>, O or (CR<sup>23</sup>R<sup>23</sup>)<sub>n</sub>, R<sup>2</sup> is optionally substituted C<sub>1-12</sub> alkyl, C<sub>2-12</sub> alkenyl, C<sub>2-12</sub> alkynyl, C<sub>3-12</sub>

carbocyclyl or C<sub>3-12</sub> heterocyclyl as defined in the first aspect.

The twelfth aspect of the invention provides an alternative process for the production of a compound of formula (VII) by the introduction of the  $X^3$  group

## 5 to a compound of formula (X).

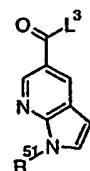


wherein  $R^{51}$  and  $L^3$  are as defined in the fourth aspect and  $X^3$  is as defined in the sixth aspect.

10 In particular where  $R^{51}$  is a silyl group, introduction of  $R^{51}$  occurs prior to the introduction of  $X^3$ . Preparation of compound of general formula (X) wherein  $L^3$  is carbocyclyl or heterocyclyl has been disclosed in GB0305142.2

Thus, a skilled person will appreciate that the actual synthetic sequence to prepare compound (VII) will depend on the type of protecting group  $R^{51}$  used, i.e. the compound (VII) can be prepared by the process of the twelfth aspect or by the processes set out in the eighth and tenth aspects.

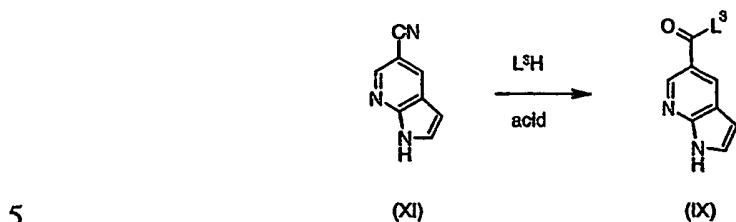
The thirteenth aspect of the invention provides a compound of formula (X)



20

wherein L<sup>3</sup> is as defined in the eleventh aspect and  
wherein R<sup>51</sup> is an amino protecting group as defined in the fourth aspect.

The fourteenth aspect of the invention provides a method for preparation of compound of formula (IX) by the acid-catalysed hydrolysis of nitrile (XI) in the presence of alcohol, preferably methanol or ethanol.

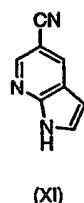


wherein  $L^3$  is OR<sup>50</sup>;

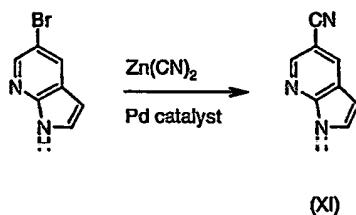
and  $R^{50}$  is as defined in the third aspect of the invention. Preferably  $R^{50}$  is methyl or ethyl.

10 The acid-catalysed hydrolysis of compound (IX) is usually carried out by refluxing alcoholic solution of (IX) containing concentrated sulfuric acid. The product is isolated by neutralisation of the reaction mixture and extraction. It can be appreciated that thus prepared (XI) is an ester.

15 The fifteenth aspect of the invention provides a compound of formula (XI)

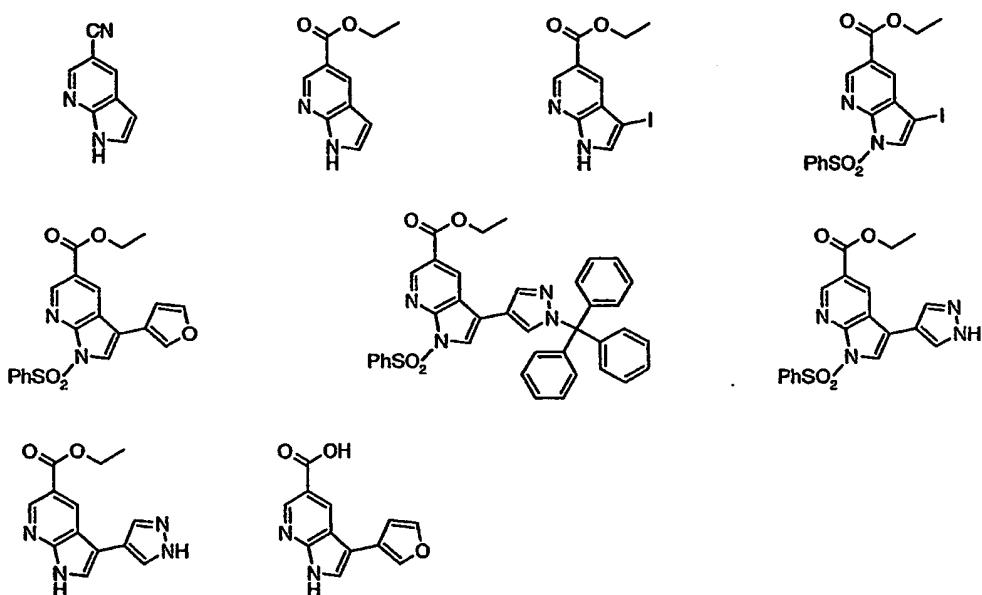


The sixteenth aspect of the invention provides a process for the manufacture of 1*H*-Pyrrolo[2,3-*b*]pyridine-5-carbonitrile (XI) comprising reaction of 5-bromo-1*H*-pyrrolo[2,3-*b*]pyridine with Zn(CN)<sub>2</sub> in the presence of a suitable palladium catalyst such as Pd(PPh<sub>3</sub>)<sub>4</sub>.



The present invention encompasses one or more compounds as defined in the third, fifth, seventh, ninth, eleventh, thirteenth and fifteenth of the invention as set out below;

5



The present invention also encompasses a process for manufacturing a compound of the first aspect, the process comprising providing a starting material, which is commercially available or can be produced by a method known in the art, converting the starting material to form an intermediate compound of the third, fifth, seventh, ninth, eleventh, thirteenth and fifteenth aspects using a process as described above or a process known in the art (and optionally converting the intermediate compound so formed into another intermediate compound) and then converting the intermediate compound into a compound of the first aspect using a process as described above or a process

known in the art (and optionally converting the compound of the first aspect so formed into another compound of the first aspect).

The seventeenth aspect of the invention provides a composition comprising a  
5 compound according to the first aspect of the invention in combination with a pharmaceutically acceptable carrier, diluent or excipient.

The composition may also comprise one or more additional active agent, such as an anti-inflammatory agent (for example a p38 inhibitor, glutamate receptor  
10 antagonist, or a calcium channel antagonist), AMPA receptor antagonist, a chemotherapeutic agent and/or an antiproliferative agent.

Suitable carriers and/or diluents are well known in the art and include pharmaceutical grade starch, mannitol, lactose, magnesium stearate, sodium  
15 saccharin, talcum, cellulose, glucose, sucrose, (or other sugar), magnesium carbonate, gelatin, oil, alcohol, detergents, emulsifiers or water (preferably sterile). The composition may be a mixed preparation of a composition or may be a combined preparation for simultaneous, separate or sequential use (including administration).

20 The composition according to the invention for use in the aforementioned indications may be administered by any convenient method, for example by oral (including by inhalation), parenteral, mucosal (e.g. buccal, sublingual, nasal), rectal or transdermal administration and the compositions adapted  
25 accordingly.

For oral administration, the composition can be formulated as liquids or solids, for example solutions, syrups, suspensions or emulsions, tablets, capsules and lozenges.

A liquid formulation will generally consist of a suspension or solution of the compound or physiologically acceptable salt in a suitable aqueous or non-aqueous liquid carrier(s) for example water, ethanol, glycerine, polyethylene glycol or oil. The formulation may also contain a suspending agent, preservative, flavouring or colouring agent.

A composition in the form of a tablet can be prepared using any suitable pharmaceutical carrier(s) routinely used for preparing solid formulations.

10 Examples of such carriers include magnesium stearate, starch, lactose, sucrose and microcrystalline cellulose.

A composition in the form of a capsule can be prepared using routine encapsulation procedures. For example, powders, granules or pellets containing the active ingredient can be prepared using standard carriers and then filled into a hard gelatine capsule; alternatively, a dispersion or suspension can be prepared using any suitable pharmaceutical carrier(s), for example aqueous gums, celluloses, silicates or oils and the dispersion or suspension then filled into a soft gelatine capsule.

20 Compositions for oral administration may be designed to protect the active ingredient against degradation as it passes through the alimentary tract, for example by an outer coating of the formulation on a tablet or capsule.

25 Typical parenteral compositions consist of a solution or suspension of the compound or physiologically acceptable salt in a sterile aqueous or non-aqueous carrier or parenterally acceptable oil, for example polyethylene glycol, polyvinyl pyrrolidone, lecithin, arachis oil or sesame oil. Alternatively, the

solution can be lyophilised and then reconstituted with a suitable solvent just prior to administration.

Compositions for nasal or oral administration may conveniently be formulated 5 as aerosols, drops, gels and powders. Aerosol formulations typically comprise a solution or fine suspension of the active substance in a physiologically acceptable aqueous or non-aqueous solvent and are usually presented in single or multidose quantities in sterile form in a sealed container, which can take the form of a cartridge or refill for use with an atomising device. Alternatively the 10 sealed container may be a unitary dispensing device such as a single dose nasal inhaler or an aerosol dispenser fitted with a metering valve, which is intended for disposal once the contents of the container have been exhausted. Where the dosage form comprises an aerosol dispenser, it will contain a pharmaceutically acceptable propellant. The aerosol dosage forms can also take the form of a 15 pump-atomiser.

Compositions suitable for buccal or sublingual administration include tablets, lozenges and pastilles, wherein the active ingredient is formulated with a carrier such as sugar and acacia, tragacanth, or gelatin and glycerin.

20 Compositions for rectal or vaginal administration are conveniently in the form of suppositories (containing a conventional suppository base such as cocoa butter), pessaries, vaginal tabs, foams or enemas.

25 Compositions suitable for transdermal administration include ointments, gels, patches and injections including powder injections.

Conveniently the composition is in unit dose form such as a tablet, capsule or ampoule.

The eighteenth aspect of the invention provides a process for the manufacture of a composition according to the seventeenth aspect of the invention. The manufacture can be carried out by standard techniques well known in the art

5 and comprises combining a compound according to the first aspect of the invention and the pharmaceutically acceptable carrier or diluent and optionally one or more additional active agents. The composition may be in any form including a tablet, a liquid, a capsule, and a powder or in the form of a food product, e.g. a functional food. In the latter case the food product itself may act

10 as the pharmaceutically acceptable carrier.

The nineteenth aspect of the present invention relates to a compound of the first aspect, or a composition of the seventeenth aspect, for use in medicine.

15 The compounds of the present invention are inhibitors of JNK, such as JNK1, JNK2, or JNK3. In particular, the compounds of the present invention are inhibitors of JNK3. Preferably, the compounds of the present invention inhibit JNK3 selectively (i.e. the compounds of the invention preferably show greater activity against JNK3 than JNK1 and 2). For the purpose of this invention, an

20 inhibitor is any compound, which reduces or prevents the activity of the JNK enzyme.

The compounds are therefore useful for conditions for which inhibition of JNK activity is beneficial. Thus, preferably, this aspect provides a compound of the

25 first aspect, or a composition of the seventeenth aspect of the present invention, for the prevention or treatment of a JNK-mediated disorder. The compounds of the first aspect of the invention may thus be used for the inhibition of JNK, more preferably for the inhibition of JNK3.

A "JNK-mediated disorder" is any disease or deleterious condition in which JNK plays a role. Examples include neurodegenerative disorder (including dementia), inflammatory disease, a disorder linked to apoptosis, particularly neuronal apoptosis, autoimmune disease, destructive bone disorder, 5 proliferative disorder, cancer, infectious disease, allergy, ischemia reperfusion injury, heart attack, angiogenic disorder, organ hypoxia, vascular hyperplasia, cardiac hypertrophy, thrombin induced platelet aggregation and any condition associated with prostaglandin endoperoxidase synthase-2. The compounds of the present invention may be used for any of these JNK-mediated disorders.

10

The compounds of the present invention are particularly useful for the prevention or treatment of a neurodegenerative disorder. In particular, the neurodegenerative disorder results from apoptosis and/or inflammation. Examples of neurodegenerative disorders are: dementia; Alzheimer's disease; 15 Parkinson's disease; Amyotrophic Lateral Sclerosis; Huntington's disease; senile chorea; Sydenham's chorea; hypoglycemia; head and spinal cord trauma including traumatic head injury; acute and chronic pain; epilepsy and seizures; olivopontocerebellar dementia; neuronal cell death; hypoxia-related neurodegeneration; acute hypoxia; glutamate toxicity including glutamate 20 neurotoxicity; cerebral ischemia; dementia linked to meningitis and/or neurosis; cerebrovascular dementia; or dementia in an HIV-infected patient.

The neurodegenerative disorder may be a peripheral neuropathy, including mononeuropathy, multiple mononeuropathy or polyneuropathy. Examples of 25 peripheral neuropathy may be found in diabetes mellitus, Lyme disease or uremia; peripheral neuropathy caused by a toxic agent; demyelinating disease such as acute or chronic inflammatory polyneuropathy, leukodystrophies, or Guillain-Barré syndrome; multiple mononeuropathy secondary to a collagen vascular disorder (e.g. polyarteritis nodosa, SLE, Sjögren's syndrome); multiple

mononeuropathy secondary to sarcoidosis; multiple mononeuropathy secondary to a metabolic disease (e.g. diabetes or amyloidosis); or multiple mononeuropathy secondary to an infectious disease (e.g. Lyme disease or HIV infection).

5

The compounds of the invention can also be used to prevent or treat disorders resulting from inflammation. These include, for example, inflammatory bowel disorder, bronchitis, asthma, acute pancreatitis, chronic pancreatitis, allergies of various types, and possibly Alzheimer's disease. Autoimmune diseases which

10 may also be treated or prevented by the compounds of the present invention include rheumatoid arthritis, systemic lupus erythematosus, glomerulonephritis, scleroderma, chronic thyroiditis, Graves's disease, autoimmune gastritis, diabetes, autoimmune haemolytic anaemia, autoimmune neutropaenia, thrombocytopenia, atopic dermatitis, chronic active hepatitis, myasthenia gravis, multiple sclerosis,

15 ulcerative colitis, Crohn's disease, psoriasis or graft vs host disease.

A compound of the present invention may be administered simultaneously, subsequently or sequentially with one or more other active agent, such as an anti-inflammatory agent e.g. p38 inhibitor, AMPA receptor antagonist,

20 glutamate receptor antagonist, calcium channel antagonist, a chemotherapeutic agent or an antiproliferative agent. For example, for acute treatment, a p38 inhibitor may be administered to a patient prior to administering a compound of the present invention.

25 The compounds of the invention will normally be administered in a daily dosage regimen (for an adult patient) of, for example, an oral dose of between 1 mg and 2000 mg, preferably between 30 mg and 1000 mg, e.g. between 10 and 250 mg or an intravenous, subcutaneous, or intramuscular dose of between 0.1 mg and 100 mg, preferably between 0.1 mg and 50 mg, e.g. between 1 and 25

mg of the compound of the formula (I) or a physiologically acceptable salt thereof calculated as the free base, the compound being administered 1 to 4 times per day. Suitably the compounds will be administered for a period of continuous therapy, for example for a week or more.

5

The twentieth aspect of the invention relates to a method of treating or preventing a JNK-mediated disorder in an individual, which method comprises administering to said individual a compound of the first aspect or a composition of the seventeenth aspect. The active compound is preferably administered in a

10 cumulative effective amount. The individual may be in need of the treatment or prevention. Any of the JNK-mediated disorders listed above in relation to the nineteenth aspect may be the subject of treatment or prevention according to the twentieth aspect. One or more other active agent may be administered to the individual simultaneously, subsequently or sequentially to administering the

15 compound. The other active agent may be an anti-inflammatory agent such as a p38 inhibitor, glutamate receptor antagonist, AMPA receptor antagonist, calcium channel antagonist, a chemotherapeutic agent or an antiproliferative agent, but is preferably p38 inhibitor for acute treatment.

20 The twenty first aspect of the present invention provides the use of a compound of the first aspect in the manufacture of a medicament for the prevention or treatment of a JNK-mediated disorder. The medicament may be used for treatment or prevention of any of the JNK-mediated disorders listed above in relation to the nineteenth aspect. Again, the compound of the present invention

25 may be administered simultaneously, subsequently or sequentially with one or more other active agent, preferably a p38 inhibitor for acute treatment.

In the twenty second aspect of the invention, there is provided an assay for determining the activity of the compounds of the present invention, comprising

providing a system for assaying the activity and assaying the activity of the compound. Preferably the assay is for the JNK inhibiting activity of the compound, more preferably it is for the JNK3-specific inhibiting activity of the compounds. The compounds of the invention may be assayed in vitro, in vivo, 5 in silico, or in a primary cell culture or a cell line. In vitro assays include assays that determine inhibition of either the kinase activity or ATPase activity of activated JNK. Alternatively, in vitro assays may quantitate the ability of a compound to bind JNK and may be measured either by radiolabelling the compound prior to binding, then isolating the inhibitor/JNK complex and 10 determining the amount of the radiolabel bound or by running a competition experiment where new inhibitors are incubated with JNK bound to known radioligands. An example of an assay, which may be used, is Scintillation Proximity Assay (SPA), preferably using radiolabelled ATP. Another example is ELISA. Any type or isoform of JNK may be used in these assays.

15

In the twenty third aspect, there is provided a method of inhibiting the activity or function of a JNK, particularly JNK3, which method comprises exposing a JNK to a compound or a composition of the first or seventeenth aspect of the present invention. The method may be performed in a research model, in vitro, 20 in silico, or in vivo such as in an animal model. A suitable animal model may be a kainic acid model in rat or mice, traumatic brain injury model in rat, or MPTP in mice.

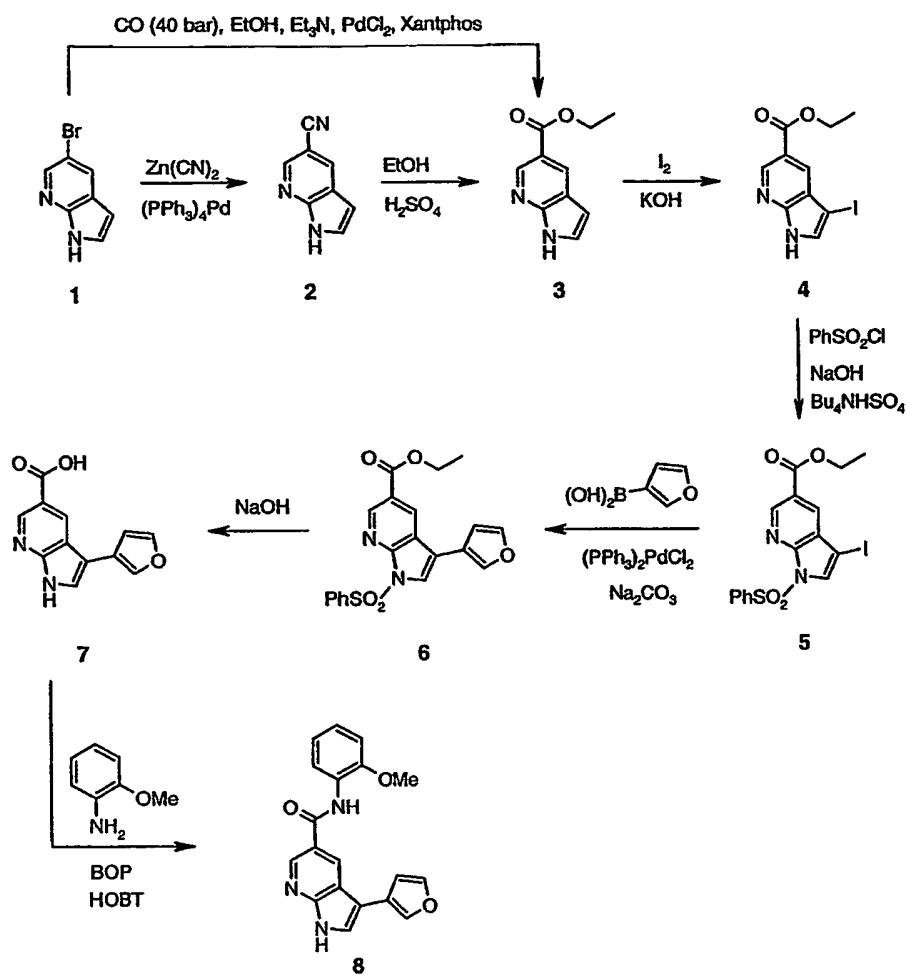
All features of each of the aspects apply to all other aspects *mutatis mutandis*.

25

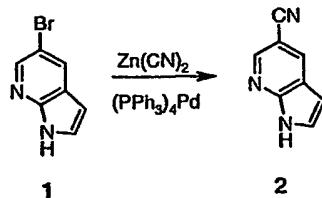
The invention will now be illustrated by the following non-limiting examples.

## EXAMPLES

## 5 Synthesis of example inhibitor 8



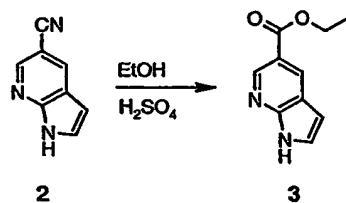
## 1H-Pyrrolo[2,3-b]pyridine-5-carbonitrile (2)



10 A mixture of bromide 1 (10.0 g, 50.8 mmol),  $ZnCl_2$  (3.58 g, 30.5 mmol), and

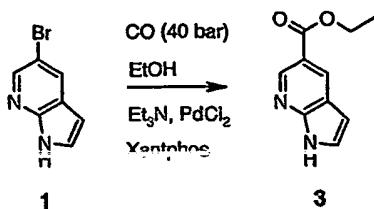
Pd(PPh<sub>3</sub>)<sub>4</sub> (3.52 g, 3.05 mmol) in DMF (110 mL) was heated at 80 °C overnight. The solvent was evaporated and the residue separated by silicagel chromatography (100 g column) using hexane:ethyl acetate as eluent (gradient elution). The resulting solid was partitioned between water (200 mL)/CH<sub>2</sub>Cl<sub>2</sub> (100 mL) and the aqueous phase extracted with more CH<sub>2</sub>Cl<sub>2</sub> (4 x 100 mL). The combined organic extracts were dried (MgSO<sub>4</sub>) and concentrated to give product 2 as a white solid (5.48 g, 75%), which was used for subsequent reactions without further purification.

10 1H-Pyrrolo[2,3-b]pyridine-5-carboxylic acid ethyl ester (3)



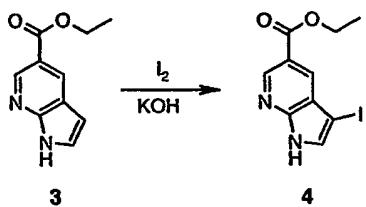
A solution of 2 (197.6 mg, 1.38 mmol) in a mixture of EtOH (4.2 mL) and concentrated H<sub>2</sub>SO<sub>4</sub> (2.0 mL) was refluxed overnight. The reaction mixture was 15 cooled and poured slowly onto a mixture of NaHCO<sub>3</sub> (8.2 g, solid), ice (50 g) and ethyl acetate (20 mL). The organic layer was separated. The aqueous layer was extracted with ethyl acetate (3x20 mL). Combined organic solutions were dried (MgSO<sub>4</sub>), concentrated and dried in vacuum to afford ethyl ester 3 (262.5 mg, 100%) as white solid; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 1.44 (t, J = 7.2 Hz, 20 3H), 4.43 (q, J = 7.2 Hz, 2H), 6.62 (dd, J = 3.6, 2.0 Hz, 1H), 7.39 (dd, J = 3.6, 2.4 Hz, 1H), 8.63 (dd, J = 2.0, 0.8 Hz, 1H), 9.01 (d, J = 2.0 Hz, 1H), 9.21 (bs, 1H).

**1H-Pyrrolo[2,3-b]pyridine-5-carboxylic acid ethyl ester (3) – an alternative method**



An autoclave charged with a mixture of **1** (9.85 g, 50.0 mmol),  $\text{PdCl}_2$  (44 mg, 0.25 mmol), Xantphos (145 mg, 0.25 mmol),  $\text{Et}_3\text{N}$  (9.0 mL, 64.6 mmol) in EtOH (55 mL) was purged with CO. Then, CO was introduced to the pressure of 40 bar and the temperature of the reaction mixture was raised to 120 °C. The mixture was stirred at 120 °C overnight. The mixture was cooled to room temperature and CO was released.  $^1\text{H}$  NMR of an aliquot showed conversion of 80%. New portion of  $\text{PdCl}_2$  (44 mg, 0.25 mmol) and Xantphos (145 mg, 0.25 mmol) was added. The autoclave was pressurized with CO again and raised to 120 °C. After additional 3 days stirring at 120 °C the reaction was completed ( $^1\text{H}$  NMR). The reaction mixture was concentrated and separated between AcOEt – saturated aqueous  $\text{NaHCO}_3$ . The aqueous layer was extracted with AcOEt (5x100 mL). Combined organic solutions were dried ( $\text{MgSO}_4$ ), and concentrated to afford **3** (7.55 g, 79%) as tan solid indistinguishable ( $^1\text{H}$  NMR) from the sample prepared via nitrile **2**.

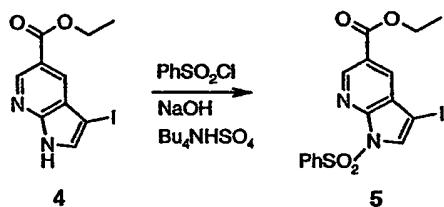
### 3-Iodo-1*H*-pyrrolo[2,3-*b*]pyridine-5-carboxylic acid ethyl ester (4)



To a solution of 3 (100 mg, 0.526 mmol) in DMF (1.3 mL) was added I<sub>2</sub> (162.56 mg, 0.64 mmol) followed by KOH (43.0 mg, 0.77 mmol). The reaction mixture was stirred for 35 min, and treated with a mixture of 0.1 M phosphate buffer (2.0 mL): saturated aqueous Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub> (0.5 mL). The suspension was

stirred at r.t. for 15 min. The solid precipitate was filtered off, washed with water (2.0 mL), and dried under high vacuum to give 4 as white solid (123.0 mg, 74%);  $^1\text{H}$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$  1.34 (t,  $J$  = 7.1 Hz, 3H), 4.35 (q,  $J$  = 7.1 Hz, 2H), 7.87 (s, 1H), 8.15 (d,  $J$  = 2.0 Hz, 1H), 8.80 (d,  $J$  = 2.0 Hz, 1H), 5 12.50 (bs, 1H).

**1-Benzenesulfonyl-3-iodo-1H-pyrrolo[2,3-b]pyridine-5-carboxylic acid ethyl ester (5)**



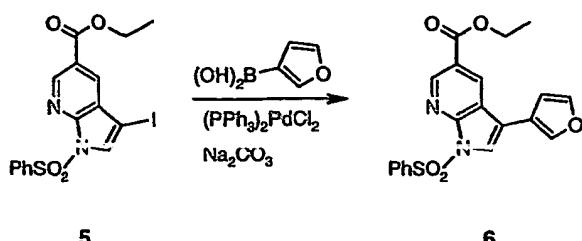
10 To a suspension of 4 (112.5 mg, 0.356 mmol) in  $\text{CH}_2\text{Cl}_2$  (2.2 mL) was added benzenesulfonyl chloride (69.6  $\mu\text{L}$ , 0.55 mmol), tetra-n-butylammonium hydrogen sulfate (14.9 mg, 0.044 mmol) and 50% aqueous NaOH (29  $\mu\text{L}$ ), and the reaction mixture was stirred for 1 h. The organic layer was separated and the residue was extracted with  $\text{CH}_2\text{Cl}_2$  (2x3 mL). The combined organic solutions were dried ( $\text{MgSO}_4$ ) and concentrated to give oil, which was triturated with methanol (1.0 mL) to give white solid. The solid was filtered off, washed with methanol (2x1 mL) and dried overnight in vacuum to give product 5 as a white solid (139.2 mg, 64%);  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  1.42 (t,  $J$  = 7.1 Hz, 3H), 4.43 (q,  $J$  = 7.1 Hz, 2H), 7.49-7.53 (m, 2H), 7.59-7.64 (m, 1H), 7.94 (s, 1H), 8.21-8.25 (m, 2H), 8.31 (d,  $J$  = 2.0 Hz, 1H), 9.08 (d,  $J$  = 2.0 Hz, 1H).

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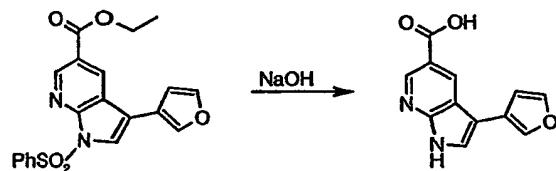
**1-Benzenesulfonyl-3-furan-3-yl-1H-pyrrolo[2,3-b]pyridine-5-carboxylic acid ethyl ester (6)**

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A mixture of 5 (100 mg, 0.219 mmol), EtOH (1.3 mL), toluene (1.3 mL), furan-3-boronic acid (37.4 mg, 0.33 mmol), 1M aq.  $\text{Na}_2\text{CO}_3$  (0.55 mL, 0.55 mmol), LiCl (28 mg, 0.66 mmol) and  $\text{PdCl}_2(\text{PPh}_3)_2$  (12.9 mg, 18.4  $\mu\text{mol}$ ) was refluxed 5 for 17 min. The organic layer was separated, brine was added, and the aqueous layer was extracted with AcOEt. The combined organic solutions were concentrated and separated by means of silicagel chromatography using hexane:CH<sub>2</sub>Cl<sub>2</sub> as eluent (in gradient up to 15% AcOEt) to give 6 as a tan solid 10 (66.8 mg, 77%); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  1.42 (t, *J* = 7.1 Hz, 3H), 4.43 (q, *J* = 7.1 Hz, 2H), 6.71 (dd, *J* = 1.8, 0.9 Hz, 1H), 7.48-7.54 (m, 2H), 7.56 (t, *J* = 1.7 Hz, 1H), 7.58-7.63 (m, 1H), 7.85 (t, *J* = 0.9 Hz, 1H), 7.89 (s, 1H), 8.22-8.27 (m, 2H), 8.60 (d, *J* = 2.0 Hz, 1H), 9.12 (d, *J* = 2.0 Hz, 1H).

### 3-Furan-3-yl-1*H*-pyrrolo[2,3-*b*]pyridine-5-carboxylic acid (7)



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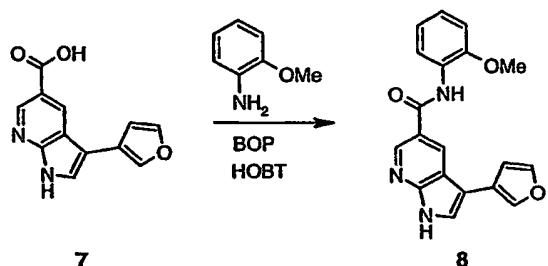
6

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To a suspension of 6 (65.5 mg, 0.165 mmol) in EtOH (1.0 mL), was added 10% aqueous NaOH (0.5 mL, about 1.25 mmol), and the reaction mixture was refluxed for 0.5 h. The mixture was cooled to r.t. and EtOH was evaporated in vacuum. The residual solution was treated with glacial acetic acid (75  $\mu$ L, 1.25 mmol). The suspension which formed was stirred at r.t. for 30 min. The solid was filtered off, washed with water, and dried under high vacuum to afford 7 as

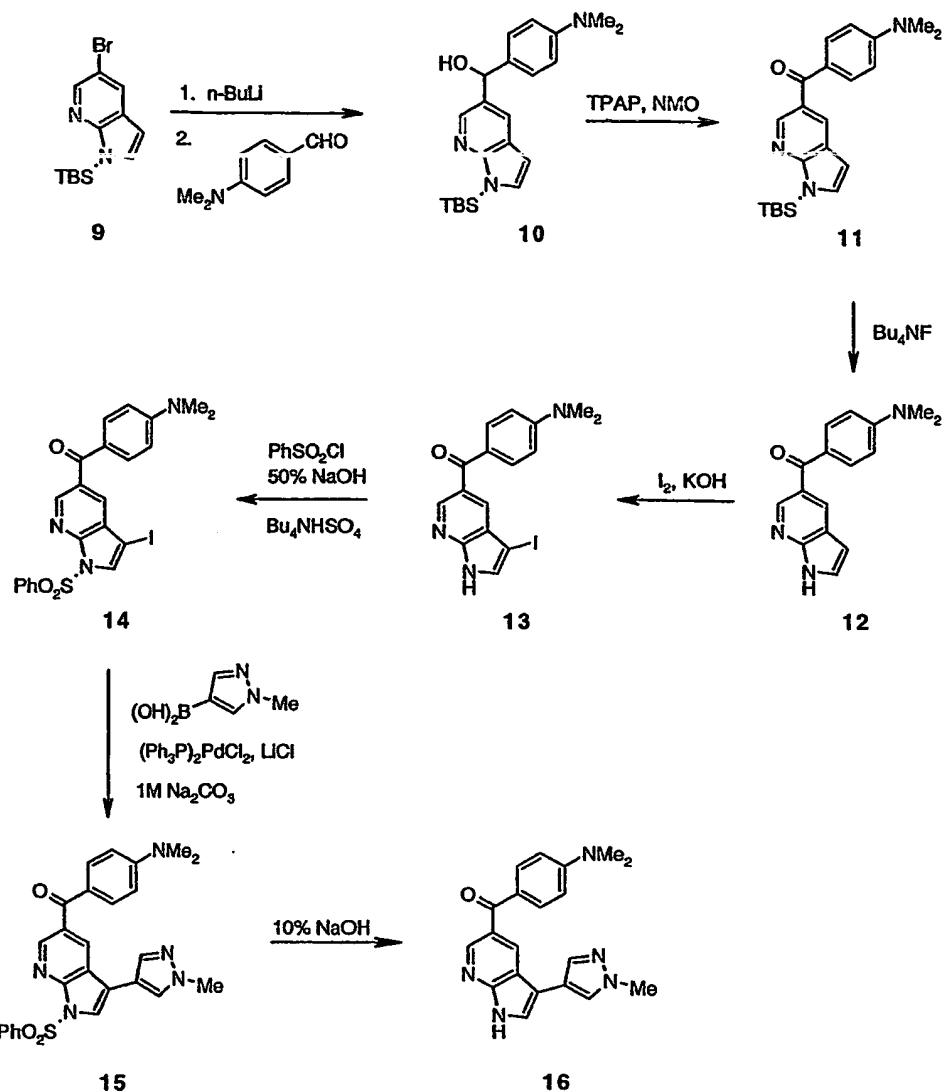
a tan powder (34.1 mg, 91 %);  $^1\text{H}$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$  6.94 (d,  $J$  = 1.7 Hz, 1H), 7.74 (t,  $J$  = 1.5 Hz, 1H), 7.88 (d,  $J$  = 2.2 Hz, 1H), 8.17 (s, 1H), 8.62 (d,  $J$  = 1.8 Hz, 1H), 8.81 (d,  $J$  = 1.8 Hz, 1H), 12.16 (bs, 1H).

5 3-Furan-3-yl-1H-pyrrolo[2,3-b]pyridine-5-carboxylic acid (2-methoxy-phenyl)-amide (8)

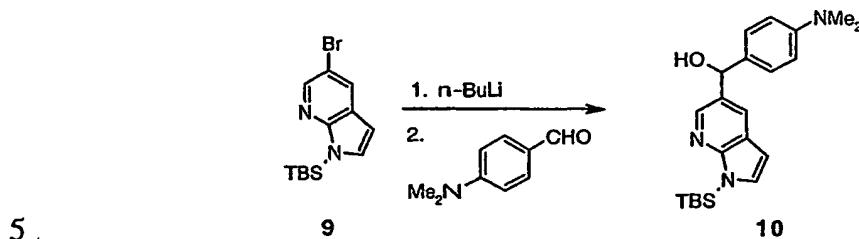


A mixture of 2-methoxy-phenylamine (21.55 mg, 0.175 mmol), carboxylic acid 7 (20 mg, 88  $\mu$ mol), BOP (50.42 mg, 0.114 mmol), HOBT (17.8 mg, 0.132 mmol) and *i*-Pr<sub>2</sub>NEt (30.7  $\mu$ L, 0.176 mmol) in dry DMF (0.6 mL) was stirred at r.t. for 2 h. Separation of the crude reaction mixture by LCMS (column LUNA 10  $\mu$  C18(2) 00G-4253-V0 250x50 mm) using water – acetonitrile (0.1% AcOH) as eluent (in gradient; flow 80 mL/min) afforded amide 8 (13.11 mg, 45%) as a white solid. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>:5%CD<sub>3</sub>OD)  $\delta$  3.93 (s, 3H), 6.71 (dd, J = 1.8, 0.8 Hz, 1H), 6.94 (dd, J = 8.0, 1.5 Hz, 1H), 7.03 (ddd, J = 7.9, 7.7, 1.5 Hz, 1H), 7.10 (ddd, J = 8.0, 7.7, 1.7 Hz, 1H), 7.50 (s, 1H), 7.53 (t, J = 1.7 Hz, 1H), 7.84 (t, J = 1.1 Hz, 1H), 8.48 (dd, J = 7.9, 1.7 Hz, 1H), 8.61 (d, J = 2.0 Hz, 1H), 8.81 (d, J = 2.0 Hz, 1H); LCMS m/e 334 (M+H), 375 (M+MeCN+H).

52



**[1-(tert-Butyl-dimethyl-silanyl)-1H-pyrrolo[2,3-b]pyridin-5-yl]- (4-dimethylamino-phenyl)-methanol (10)**

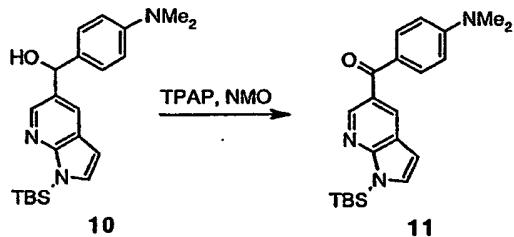


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To a -78 °C stirred solution of the bromo-azaindole **9** (2 g, 6.4 mmol; preparation disclosed in WO2004/078757) in THF (10 mL) was added a 2.5 M solution of *n*-butyllithium in hexanes (5.4 mL, 13.5 mmol) dropwise. The resulting yellow solution was stirred for 0.6 h at -78 °C and then 4-5 dimethylamino-benzaldehyde (1.25 g, 8.4 mmol) in THF (10 mL) was added slowly. The mixture was allowed to warm to room temperature and after a further 20 h diluted with EtOAc and saturated brine and partitioned. The aqueous layer was extracted with EtOAc (2x). The combined organic solutions were dried ( $\text{MgSO}_4$ ) and concentrated *in vacuo*. The crude residue was purified 10 by silica gel chromatography employing  $\text{Et}_3\text{N}$ -impregnated silica and  $\text{AcOEt}$ :hexane as eluent (gradient) to afford a 2.5:1 mixture of the alcohol **10** and 4-dimethylamino-benzaldehyde (1.63 g, 47%) as a yellow oil. The partially purified alcohol **10** was used directly for the next step without any further purification.

15

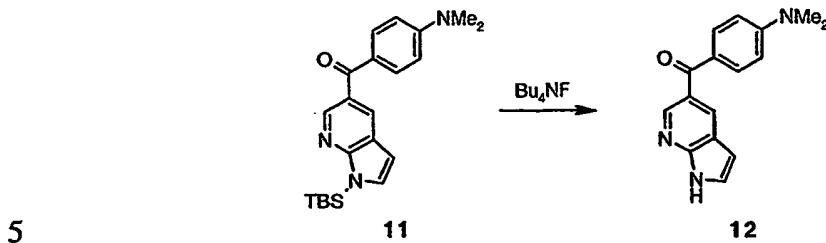
**[1-(tert-Butyl-dimethyl-silanyl)-1H-pyrrolo[2,3-b]pyridin-5-yl]-[4-dimethylamino-phenyl]-methanone (11)**



To a stirred solution of a 2.5:1 mixture of alcohol **11** and 4-dimethylamino-20 benzaldehyde (1.23 g, 2.3 mmol), 4-methylmorpholine N-oxide (0.41 g, 3.5 mmol), 4A powdered molecular sieves (1.2 g) in  $\text{CH}_2\text{Cl}_2$  (12 mL) was added TPAP (82 mg, 0.23 mmol) in one portion. After 3 h the mixture was filtered through a pad of silica and the silica pad washed with  $\text{CH}_2\text{Cl}_2$ . The combined organic solutions were concentrated to afford **11** as black oil that was used 25 directly in the next step without any purification.  $^1\text{H}$  NMR (400 MHz;  $\text{CDCl}_3$ )  $\delta$  0.66 (s, 6H), 0.95 (s, 9H), 3.09 (s, 6H), 6.62 (*d*, *J*= 3.5 Hz, 1H), 6.70 (*d*, *J*= 9.2

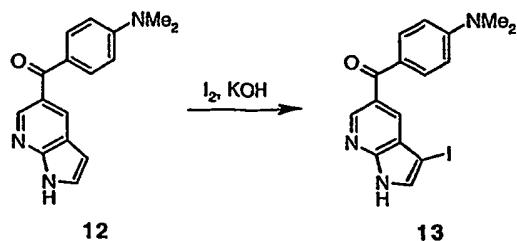
Hz, 2H), 7.31 (*d*, *J*= 3.5 Hz, 1H), 7.83 (*d*, *J*= 9.1 Hz, 2H), 8.27 (*d*, *J*= 2.1 Hz, 1H) and 8.71 (*d*, *J*= 2.1 Hz, 1H).

**(4-Dimethylamino-phenyl)-(1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)-methanone (12)**



To a stirred solution of the crude ketone **11** (assumed 880 mg, 2.3 mmol) in THF (13 mL) was added 1M TBAF in THF (3.5 mL, 3.5 mmol) dropwise. After 3 h the mixture was concentrated to dryness and diluted with AcOEt and saturated brine, and partitioned. The aqueous layer was extracted with AcOEt (3x) and the combined organic extracts dried ( $\text{MgSO}_4$ ), filtered and concentrated *in vacuo*. The residue was purified by silica gel chromatography using hexane:AcOEt (gradient elution) to afford ketone **12** (298 mg, 48% over 2 steps).  $^1\text{H}$  NMR (400 MHz;  $\text{CDCl}_3$ )  $\delta$  3.10 (s, 6H), 6.62 (d,  $J$  = 3.4 Hz, 1H), 6.72 (d,  $J$  = 9.0 Hz, 2H), 7.42 (d,  $J$  = 3.3 Hz, 1H), 7.84 (d,  $J$  = 9.0 Hz, 2H), 8.38 (d,  $J$  = 1.9 Hz, 1H), 8.78 (d,  $J$  = 1.9 Hz, 1H) and 10.06 (brs, 1H).

**(4-Dimethylamino-phenyl)-(3-iodo-1H-pyrrolo[2,3-b]pyridin-5-yl)-methanone (13)**

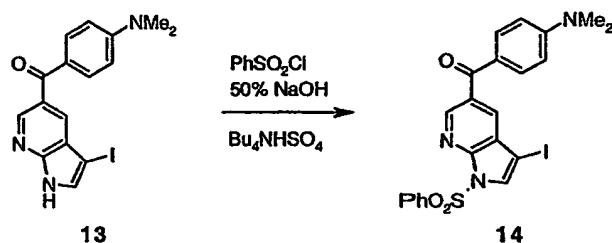


20 To a stirred solution of the ketone 12 (295 mg, 1.1 mmol) in DMF (7.5 mL) was added potassium hydroxide pellets (235 mg, 4.2 mmol). After 0.3 h, iodine (254 mg, 1.0 mmol) was added in one portion. Following a further 5 h the

mixture was diluted with AcOEt and saturated sodium thiosulfate, and stirred vigoursly for 5 minutes. The mixture was partitioned and the aqueous layer extracted with AcOEt (3x). The combined organic extracts were dried ( $\text{MgSO}_4$ ), filtered and concentrated *in vacuo* to afford iodide **13** as brown solid

5 that was used directly in the next step without any purification.

**(1-Benzenesulfonyl-3-iodo-1H-pyrrolo[2,3-b]pyridin-5-yl)-(4-dimethylamino-phenyl)-methanone (14)**

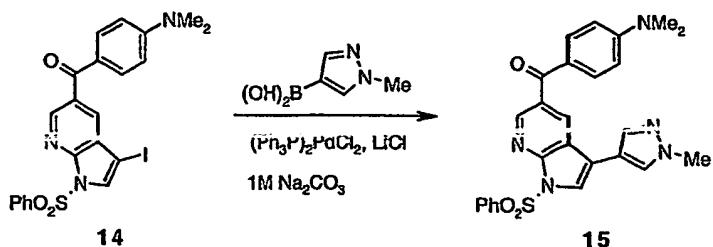


10 To a stirred solution of the iodide **13** (assumed 435 mg, 1.1 mmol) in  $\text{CH}_2\text{Cl}_2$  (13 mL) was added benzenesulfonyl chloride (304 mg, 1.7 mmol), 50% NaOH (1 mL) and *n*-tetra-*n*-butyl ammonium sulfate (57 mg, 0.17 mmol). After 4.5 h the mixture was diluted with AcOEt and saturated sodium hydrogen carbonate solution and partitioned. The aqueous layer was extracted with EtOAc (3x) and

15 the combined organic extracts were dried ( $\text{MgSO}_4$ ), filtered and concentrated *in vacuo*. The residue was treated with MeOH and stirred vigoursly for 0.5 h and then vacuum filtered to afford the iodide **14** (410 mg, 69% over 2 steps) as a tan solid.  $^1\text{H}$  NMR (400 MHz;  $\text{CDCl}_3$ )  $\delta$  3.10 (s, 6H), 6.69 ( $J$ = 9.1 Hz, 2H), 7.51 (m, 2H), 7.62 (tt,  $J$ = 1.2, 1.9 and 7.5 Hz, 1H), 7.77 (d,  $J$ = 9.1 Hz, 2H), 7.95 (s, 20 1H), 8.04 (d,  $J$ = 1.9 Hz, 1H), 8.23 (m, 2H), 8.79 (d,  $J$ = 1.9 Hz, 1H).

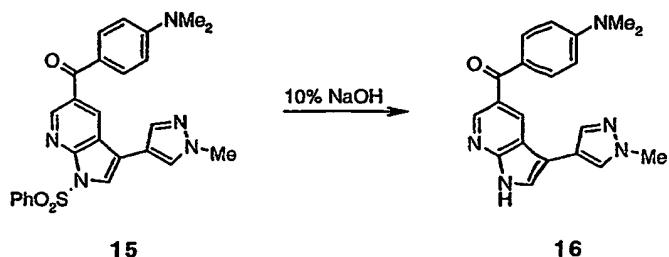
**[1-Benzenesulfonyl-3-(1-methyl-1H-pyrazol-4-yl)-1H-pyrrolo[2,3-b]pyridin-5-yl)-(4-dimethylamino-phenyl)-methanone (15)**

## 56



A mixture of iodide **14** (100 mg, 0.19 mmol), 1-methyl-1H-pyrazole-4-boronic acid (36 mg, 0.28 mmol), lithium chloride (24 mg, 0.56 mmol), dichlorobis(triphenylphosphine)-palladium (II) (7 mg, 0.01 mmol), 1M sodium 5 carbonate (0.47 mL, 0.47 mmol) in toluene (2 mL) and ethanol (2 mL) was heated at 105 °C for 6 h. Then, the reaction mixture was cooled to room temperature and partitioned between AcOEt and saturated brine. The aqueous layer was extracted with AcOEt (3x). The combined organic extracts were dried (MgSO<sub>4</sub>), filtered and concentrated. The residue was purified by preparative 10 TLC using hexane:AcOEt=1:1 (v/v) as eluent to afford ketone **15** (51 mg, 56%). <sup>1</sup>H NMR (400 MHz; CDCl<sub>3</sub>) δ 3.10 (s, 6H), 3.98 (s, 3H), 6.67 (d, *J*= 9.1 Hz, 2H), 7.51 (m, 2H), 7.59 (m, 1H), 7.69 (s, 1H), 7.79 (m, 3H), 7.86 (s, 1H), 8.23 (m, 2H), 8.36 (d, *J*= 1.9 Hz, 1H) and 8.81 (d, *J*= 1.9 Hz, 1H).

15 (4-Dimethylamino-phenyl)-[3-(1-methyl-1H-pyrazol-4-yl)-1H-pyrrolo[2,3-b]pyridin-5-yl]-methanone (**16**)



To a solution of the ketone **15** (51 mg, 0.11 mL) in ethanol (10 mL) was added 10% sodium hydroxide (1 mL) and the mixture stirred at 90 °C for 3 h. The 20 mixture was concentrated to remove ethanol and partitioned between AcOEt and saturated brine. The aqueous layer was extracted with AcOEt (3x). The

combined organic extracts were dried ( $\text{MgSO}_4$ ), filtered and concentrated. The residual orange oil was purified by preparative TLC with  $\text{AcOEt}$  as eluent to afford inhibitor 16 (14 mg, 39%).  $^1\text{H NMR}$  (400 MHz;  $\text{CDCl}_3$ )  $\delta$  3.10 (s, 6H), 3.98 (s, 3H), 6.72 (d,  $J$ = 9.1 Hz, 2H), 7.50 (d,  $J$ = 2.0 Hz, 1H), 7.68 (s, 1H), 7.76 5 (s, 1H), 7.86 (d,  $J$ = 9.1 Hz, 2H), 8.51 (d,  $J$ = 1.9 Hz, 1H), 8.78 (d,  $J$ = 1.9 Hz, 1H) and 10.28 (brs, 1H).

## Biological activity

JNK1, JNK2, JNK3 - SPA assay

5

1. Compound is dissolved in DMSO to a convenient concentration and this is diluted in 10% DMSO to a five times concentrate of the desired starting concentration (frequently 1:100).
2. 10 µl of 500 mM EDTA is added to alternative wells of the Opti-plate row, which will receive kinase reaction plus DMSO. This creates the negative control.
3. For the JNK2 and JNK3 assay, compounds are prepared in six 2-fold dilutions with water and each concentration is tested in duplicate. For the JNK1 assay compounds are prepared in four 5-fold dilutions with water which are tested in triplicate. Controls are treated identically.
4. 20 µl per well of each compound concentration is transferred to an Opti-plate, in duplicate.
5. 30 µl (JNK2/3 SPA) or 50 µl (JNK1 SPA) of substrate solution (25 mM HEPES pH 7.5, 10mM magnesium acetate with 3.33µM ATP (JNK2/3) or 2µM ATP (JNK1), approximately 7.5 kBq [ $\gamma$ -<sup>33</sup>P] ATP, GST-c-Jun, in water) is added to each well.
6. 50 µl (JNK2/3 SPA) or 30 µl (JNK1 SPA) of kinase solution (JNK in 25 mM HEPES pH 7.5, 10mM Mg Acetate) is added to each well.

Kinase	Kinase per well (µg)	GST-c-Jun per well (µg)
JNK1	0.25	1

JNK2	0.2	1.2
JNK3	0.16	1.2

7. The plate is incubated for 30 minutes at room temperature.

8. 100  $\mu$ l of bead/stop solution is added to each well (5 mg/ml glutathione-PVT-SPA beads, 40 mM ATP in PBS).

9. Plates are sealed and incubated for 30 minutes at room temperature, 5 centrifuged for 10 minutes at 2500g and counted.

10. The IC<sub>50</sub> values are calculated as the concentration of the compound being tested at which the phosphorylation of c-Jun is decreased to 50% of the control value. Example IC<sub>50</sub> values for the compounds of this invention are given in Table 1.

10

p38 ELISA

Active p38 kinase (100 ng; Upstate) was added to 2  $\mu$ g GST-ATF2 substrate (NEB) in 250 mM Hepes pH 7.5/100 mM MgAc/50  $\mu$ M ATP (final) in the 15 presence or absence of compounds in 50  $\mu$ l. The mixture was incubated at 30°C for 1 hour, and then diluted with 200  $\mu$ l PBS-Tween (0.05 %). From this, duplicate volumes of 100  $\mu$ l were added to a Reacti-Bind glutathione coated plate (Pierce) and incubated for 1 hour. After washing 3 times with PBS-Tween (0.05 %), rabbit anti-phospho-ATF2 (Thr71) antibody (NEB) was added 20 at 1:500, and incubated for another hour at room temperature. After 3 additional washes with PBS-Tween (0.05 %), 100  $\mu$ l of anti-rabbit IgG alkaline phosphatase-conjugated secondary antibody (Sigma) was added at 1:1000, the reaction was incubated for a further hour, washed 3 times, and then phosphatase substrate (Sigma) was added (100  $\mu$ l per well; 3 tablets in 5 ml water). After 25 incubation in the dark at 37°C for 1 hour, the reaction mixture was transferred

to a clear 96 well plate, and the absorbance at 405 nm was read. The  $IC_{50}$  values are calculated as the concentration of the compound being tested at which the phosphorylation of ATF2 is decreased to 50% of the control value. Example  $IC_{50}$  values for the compounds of this invention are given in Table 1 (last 5 column).

Table 1.  $IC_{50}$  values for selected compounds against JNK1, JNK2, JNK3, and p38 MAP kinase

<u>Compound</u>	JNK3 $IC_{50}$ (nM)
	<500
	<500
	<1000
	<500

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